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Combining in Silico Tools with Multicriteria Analysis for Alternatives Assessment of Hazardous Chemicals: A Case Study of Decabromodiphenyl Ether Alternatives

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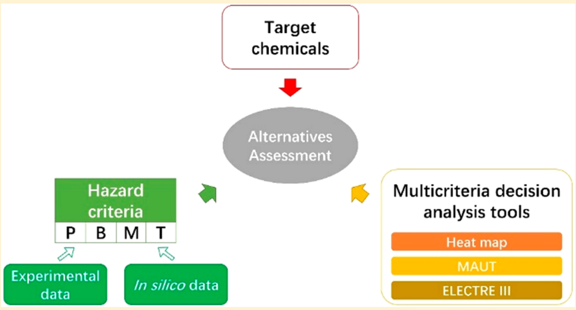
Supporting Information



ABSTRACT: Alternatives assessment is applied for minimizing the risk of unintentionally replacing a hazardous chemical with another hazardous chemical. Central challenges are the diversity of properties to consider and the lack of high-quality experimental data. To address this, a novel alternatives assessment procedure was developed based on in silico data and multicriteria decision analysis (MCDA) methods. As a case study, 16 alternatives to the flame retardant decabromodiphenyl ether were considered. The hazard properties included persistence (P), bioaccumulation potential (B), toxicities (T), and mobility in water (M). Databases were consulted and 2866 experimental data points were collected for the target chemicals; however, these were mostly replicate data points for some hazard criteria for a subset of alternatives. Therefore, in silico data and three MCDA strategies were tested including heat mapping, multiattribute utility theory (MAUT), and *Elimination Et Choix Traduisant la REalité* (ELECTRE III). The heat map clearly showed that none of the target chemicals are hazard-free, whereas MAUT and ELECTRE III agreed on ranking the "least worst" choices. This study identified several challenges and the complexity in the alternatives assessment processes motivating more case studies combining in silico and MCDA approaches.

■ INTRODUCTION

With increasingly stringent chemical regulations[1,2] as well as pressure from the public regarding the safe use of chemicals, tools to facilitate the identification of potentially hazardous substances prior to use are needed. These tools would facilitate responsible management of such hazardous substances as well as help identify safer alternatives. However, the process of alternatives assessment is not trivial. There are several examples of regrettable substitution where one hazardous chemical has been substituted by another problematic chemical, such as the substitution of bisphenol A with other bisphenols (e.g., bisphenol S, bisphenol AF, and fluorene-9-bisphenol, etc.) of which some have been identified as endocrine disruptors.[3,4] Another is the choice of *n*-hexane to replace chlorinated solvents for the automotive cleaning industry; this was later reported to be neurotoxic.[5] *N*-vinyl formamide, which requires toxic hydrogen cyanide during synthesis, was chosen as a substitute for the neurotoxic acrylamide in manufacturing polymers for water treatment.[6] Alternatives assessments of chemicals are typically performed using a broad, established framework such as the Design for the Environment (DfE) Program,[7] Cleaner technologies substitutes assessment (CTSA),[8] BizNGO with GreenScreen,[9] and Interstate Chemicals Clearinghouse (IC2),[10] that considers substances with the same or similar uses, considering both environmental and human health aspects.[11−14] A complete alternatives assessment framework would evaluate not only hazard and exposure parameters, but also life-cycle impacts, technical performance, and costs.[15] In addition, a decision-aiding component is needed to integrate and balance all these factors, so that all aspects including stakeholder perspectives are considered. Since the 1990s, several alternatives assessment frameworks have been developed and implemented.[15] Regarding the hazard assessment component, almost all frameworks take human health and ecological effects into consideration by including chemical persistency (P), bioaccumulation potential (B), and toxicity (T) properties.[15]

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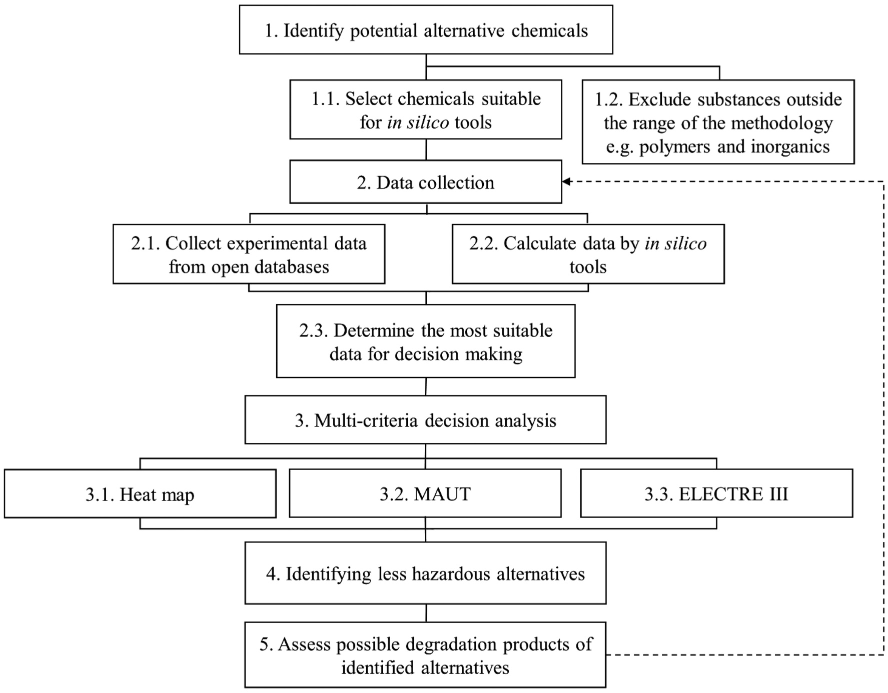


Figure 1. Work flow of the developed alternatives assessment procedure.

More recently, arguments have been presented that chemical mobility in water (M) is an important property. Chemical risk assessment used to focus more on nonpolar compounds in particular, due to their bioaccumulation potential, while polar organic chemicals sorb less to organic matter in soils and sediment, and therefore, they are more mobile in aquatic environments. Compounds that are persistent and mobile can reach aquatic biota in surface waters, and even reach drinking water resources, potentially leading to chronic human exposure. Therefore, a PMT assessment should be considered in addition to the widely used PBT assessment.[16−20]

When estimating chemical hazards, experimental data are often unavailable, especially if alternatives are newly introduced on the market and the production volumes are low. Thus, alternatives assessment processes are often hampered by large data gaps.[6] To fill these gaps, in silico tools, for example, quantitative structure−activity relationship (QSAR) models or "read-across" approaches could be used. A QSAR is a regression model where chemical descriptors reflecting key physicochemical and structural features of chemicals are correlated with a biological or toxicological activity, which can be considered a subset of read-across approaches. Read-across also refers to quantitative and qualitative methods but is more general because a "read-across" may rely on relatively sparse data which do not support complicated predictive modeling.[21] In silico tools have the advantage of providing a large amount of data with much lower cost and time requirements. Uncertainties in in silico data are generally higher compared with experimental data; however, such data are useful especially at the screening level, if certain model conditions are fulfilled including assessment of the applicability domain.[2,22,23]

Alternatives assessment frameworks demand the comparison of diverse sets of criteria; but do not necessarily provide an approach for this. For decision making based on multiple and conflicting criteria, Multicriteria Decision Analysis (MCDA) methods provide an option, drawn from operations research.[24] MCDA is commonly used in the business sector, but it has also proved itself useful for several environmental management applications.[25−31] The two major kinds of MCDA methods are synthesizing criterion methods and synthesizing preference relational systems.[32] Synthesizing criterion methods include those based on multiattribute utility theory (MAUT),[33] which requires all criteria to be converted into comparable scales, and a trade-off weighting factor representing the relative significance of each criterion to be assigned in order to permit aggregation. Synthesizing preference relational systems, such as the *Elimination Et Choix Traduisant la REalité* (ELECTRE III) method,[34] compare the performance of pairs of alternatives with respect to each criterion, and build a "credibility matrix" which presents the extent to which an alternative outranks the other alternatives. Importance coefficients are used instead of trade-off weights.

In recent years, a number of brominated flame retardants (BFRs) have been replaced after being banned or restricted for certain applications.[35,36] A review claimed that the adverse environmental and human health impacts caused by certain BFRs might even be greater than their fire safety benefits.[37] One example is decabromodiphenyl ether (decaBDE) that has been used in different products and materials including electric equipment, electronics, vehicles, furniture, and textiles since 1970s, but was later found to be persistent in the environment,[38] bioaccumulative,[39] and to induce adverse effects on both human health and other species.[2,40−43] DecaBDE has been banned in the EU since 2008 for use in electronic and electric applications[44−46] and listed by the Stockholm Convention on Persistent Organic Pollutants (Annex A).[47] In the U.S., both producers and importers announced in 2010 that they would voluntarily phase out decaBDE by the end of 2013.[48] However, years after the phase-out, decaBDE has still been identified in recently purchased electronics.[49]

Some other BFRs have been used as alternatives to decaBDE, such as decabromodiphenyl ethane (DBDPE). However, this substance was later found to also be persistent,[50−53] bioaccumulative,[54−56] potentially toxic,[36] and could arguably be considered another example of regrettable substitution. One large class of flame retardants widely used to replace BFRs is the organophosphorus flame retardants (OPFRs). Although some studies show that these OPFRs are generally safer than BFRs,[36] many studies also point out that some OPFRs are persistent, have the potential for long-range transport,[57] and can be neurotoxic.[58,59]

Herein, a new alternatives assessment procedure based on the combination of in silico approaches and MCDA is developed (Figure 1), using alternatives to decaBDE as a test case. A variety of human health and environmental hazards were in focus. This included the mobility hazard, which to our knowledge has never been used within alternatives assessments. The approach presented here is based on open source data and models, and aims at deriving a transparent tool for a first phase alternatives assessment, which evaluates the hazardous properties of chemicals.

■ MATERIALS AND METHODS

The developed alternatives assessment procedure is summarized in Figure 1. A thorough alternatives assessment should consider both the hazard of parent compounds and their possible transformation products. In this study, we focused on the parent compounds as the case chemicals and proceeded through the first three steps: alternative chemical identification; data collection; and multicriteria decision aiding.

Case Chemical Identification and Characterization. A set of potential alternatives to decaBDE was identified using literature sources[60,61] and reports from the EU,[45,46] United States Environmental Protection Agency (USEPA),[54] and one from the U.S. National Research Council.[6] A database was established with chemical names, CAS numbers, and molecular structures represented by simplified molecular input line entry specification (SMILES). Alternatives to decaBDE include a large range of chemicals, but here we focused on organic chemicals and avoided metals and polymers, due to the lack of data and in silico tools for these types of substances. Details on how chemicals were selected can be found in Section 1 of the Supporting Information (SI).

Data Collection. The variation among the chemical properties was studied using principal component analysis (PCA) and a set of 65 chemical descriptors.[62] The descriptors were derived using the MOE software[63] based on 2D structures. In addition, selected physicochemical properties were calculated by EPISUITE.[64] The octanol−water partition coefficient was derived in EPISUITE and by two alternative models in VEGA.[65]

Experimental data were acquired using the OECD QSAR Toolbox,[66] which contains five databases for physicochemical properties, 12 databases for environmental fate and transport parameters, six databases for ecotoxicity, and 39 databases for human toxicity data. Among these databases, the ECHA database of the REACH registration dossiers is one of the most important, being populated with experimental data and some modeling data on chemical properties and toxicity for substances registered under REACH as provided by registrants who manufacture or import the substance within the European Union.[2] Registered experimental data was acquired directly from the ECHA Web site.[67]

The in silico-based data were derived using several open source software packages or platforms including EPISUITE, VEGA, TEST,[68] and OECD QSAR Toolbox.[66] Results from the USEPA organized Collaborative Estrogen Receptor Activity Prediction Project (CERAPP)[69] and Collaborative Modeling Project for Androgen Receptor Activity (CoMPARA)[70,71] were also included. Six models on the OCHEM platform[72] were included. Details on the assessment criteria and in silico models are given in Table 1.

Table 1. In Silico Models Used for the Alternatives Assessment in This Study

aspects		assessment criteria	number of models	software or platforms
P		air half-life	1	EPISUITE (fugacity model)
		water half-life	1	EPISUITE (fugacity model)
		soil half-life	1	EPISUITE (fugacity model)
		sediment half-life	1	EPISUITE (fugacity model)
		biodegradation	1	EPISUITE (Biowin 3)
B		BCF	3	VEGA, EPISUITE
T	human toxicity	mutagenicity	4	VEGA
		carcinogenicity	3	VEGA
		developmental toxicity	2	VEGA
		estrogen binding	5	VEGA, OCHEM, CERAPP
		androgen binding	4	OCHEM, COMPARA
		transthyretin binding	1	OCHEM
		skin sensitization	1	VEGA
		skin irritation	1	OECD QSAR Toolbox
		eye irritation	1	OECD QSAR Toolbox
		rat oral LD50	3	TEST
	eco toxicity	fish acute LC50	8	VEGA, TEST
		Daphnia magna LC50 48h	7	VEGA, TEST
		T. pyriformis IGC50 48h	4	TEST
M		log K_{oc}	3	VEGA, EPISUITE

Decision Making Approaches with MCDA Methods. The obtained human health and environmental hazard parameters were used as 20 assessment criteria within three MCDA strategies: heat mapping, MAUT, and ELECTRE III. These criteria were selected to reflect legislative requirements (e.g., REACH), criteria used in common alternatives assessment frameworks, and availability of in silico tools. For the heat map, the range of each criterion was divided into four intervals, and each interval was color-coded (red, orange, yellow, or green—from hazardous to benign) to aid visual interpretation. Regulatory or proposed thresholds of the assessment criteria were obtained from various sources, including EU legislation, USEPA regulations, GreenScreen rules, etc. The details on how the thresholds of the four intervals were determined for each criterion are presented in Section 2 of the SI.

For the MAUT approach, each criterion was scaled from 0 (worst) to 1 (best) based on the average result of all models for that criterion. After the scaling, partial scores for P, B, T, and M properties were calculated by multiplying each criterion relevant to an aspect with the same weight. Final scores were calculated by treating the composite criteria of either PBT, PMT, or PBMT as equally important (SI Table S4).

For ELECTRE III, the calculation was done in a manner consistent with other publications.[32,73,74] Thresholds were set and pairwise comparisons were conducted on each assessment criterion. Partial scores were calculated for P, B, M, and T (SI Table S5−S8), and final scores were also calculated by treating PBT, PMT, or PBMT equally important (SI Table S9−S11).

RESULTS AND DISCUSSION

Database of DecaBDE Alternatives. In total, 31 alternatives to decaBDE including polymers and inorganic chemicals have been identified and assessed by various agencies (Table 2, SI Table S1). Among the alternatives, 17 including decaBDE were defined as suitable for the considered assessment, as they were organic compounds for which the available in silico tools applied in this study could be used. The 17 substances include 10 brominated and 1 chlorinated FR (CFR), five OPFRs (two brominated and three non-halogenated), and melamine. Their chemical names, abbreviations, CAS numbers, molecular structures, and selected physicochemical properties are listed in Table 2 and SI Table S2.

Table 2. Names of Studied Chemicals with Their Abbreviations and Chemical Abstract Service (CAS) Registry Numbers

name	abbreviation[a]	CAS number
decabromodiphenyl ether	decaBDE	1163−19−5
decabromodiphenyl ethane	DBDPE	84852−53−9
ethylene bis-tetrabromophthalimide	EBTEBPI	32588−76−4
tetrabromobisphenol A bis (2,3-dibromopropyl) ether	TBBPA-BDBPE	21850−44−2
tris(tribromophenoxy) triazine	TTBP-TAZ	25713−60−4
1,2-bis(pentabromophenoxy) ethane	BPBPE[b]	61262−53−1
2-ethylhexyl tetrabromobenzoate	EH-TBB	183658−27−7
bis(2-ethylhexyl) tetrabromophthalate	BEH-TEBP	26040−51−7
tetradecabromodiphenoxybenzene	4′-PeBPOBDE208	58965−66−5
Bis(tribromophenoxy) ethane	BTBPE	37853−59−1
bis(hexachlorocyclopentadieno) cyclooctane	DP	13560−89−9
tris(tribromoneopentyl) phosphate	TTBNPP	19186−97−1
triphenyl phosphate	TPHP	115−86−6
resorcinol bis(diphenyl phosphate)	PBDPP	57583−54−7
bisphenol A diphenyl phosphate	BPA-BDPP	5945−33−5
tris(2-bromoethyl) phosphate	TBEP[b]	27568−90−7
melamine	MA[b]	108−78−1

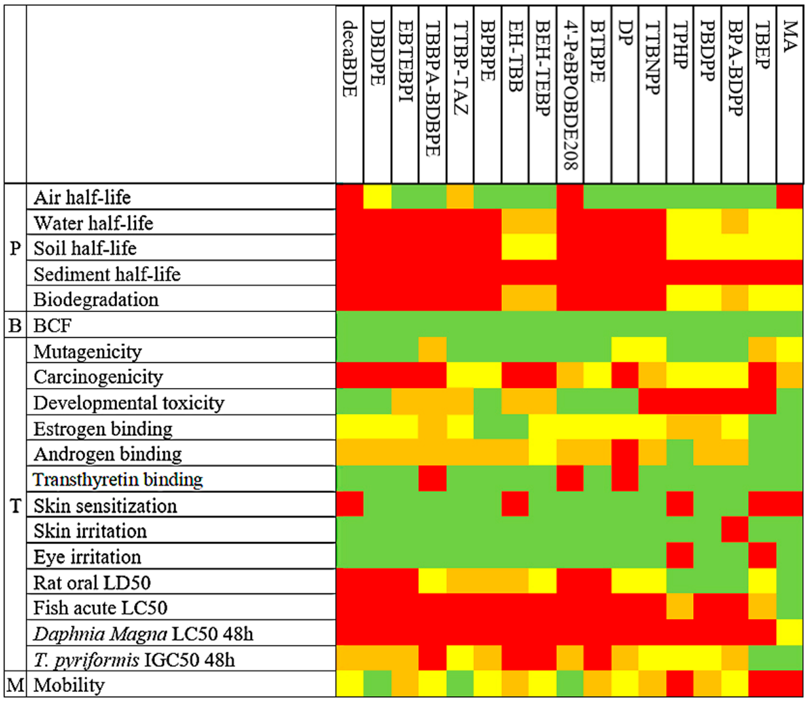
[a]Abbreviations taken from Bergman et al.[75] [b]Abbreviations defined by the authors (not covered by Bergman et al.[75]).

Structural and Chemical Property Variation. The average molecular weight of the flame retardants was 766 with a large range spanning from 126 for melamine to 1367 for 4′-PeBPOBDE208 (for comparison, decaBDE is 959). DecaBDE has a very low vapor pressure of 6.3×10^{-10} Pa at 25 °C, this is in the middle range of the alternative FRs, ranging from 4.9×10^{-18} Pa (4′-PeBPOBDE208) to 1.3×10^{-3} Pa (TBEP). The estimated octanol−water partition coefficients (log K_{ow}) are ranging from melamine (−0.4), OPFRs (2.3−9.6) to halogenated FRs (7.2−14.2) (decaBDE (10.4)). The chemical variation of the FRs, including decaBDE, was analyzed in more detail using calculated chemical descriptors and PCA, see SI Section 3.

Experimental Data. Experimental data identified in the OECD QSAR Toolbox included 2866 experimental data points (SI Table S12). Despite the large amount of data, a large proportion was only relevant to a few chemicals, and rarely for the same property across different chemicals. For example, 513 data points were collected for melamine and 275 for decaBDE, while no data were found for five of the target FRs (BPBPE, EH-TBB, PBDPP, 4′-PeBPOBDE208, and TBEP). There were 769 data points for eight FRs for repeated dose toxicity for human health hazard assessment, but no data for neurotoxicity. Another issue with these data is they do not allow for systematic comparisons across substances. For example, 843 data points were found for aquatic toxicity of our target FRs, though covering diverse indicators, such as behavior, body size, DNA damage, or lethality. The ECHA database of REACH dossiers was the largest source of OECD data. Additional, more recent data was also obtained directly from REACH dossiers.[67] Even this additional data were far from sufficient in closing data gaps (SI Section 4 and Table S13). Further, the reliability of data in REACH dossiers has been criticized in general[76,77] and for flame retardants specifically,[56] in which the majority of REACH dossiers have been reported as “partly or substantially not compliant”[76] or contain significant data gaps and data quality issues.[56,77] In summary, the collected experimental data is thus not a complete nor suitable source of information for a first tier alternatives assessment.

In Silico Data. The analyzed in silico data are shown in SI Table S14. Among the 20 criteria listed in Table 1, 17 of them (85%) had assessment results for all 17 chemicals. Among the in silico data, six (1.8%) data gaps had to be filled in manually for the alternatives assessment, of which four could be filled in by the experimental data from the ECHA database. Read-across was applied to fill in the remaining two data gaps as explained in SI Section 5. The largest number of QSAR models were available for fish and *Daphnia magna* and acute toxicity (seven and eight, respectively), whereas skin sensitization, skin and eye irritation, and persistence criteria including biodegradation and half-lives for four different environmental compartments had only one model for each criterion. The 20 criteria populated by in silico data cover most of the hazard criteria concerned by REACH[2] as well as the most well-known alternatives assessment frameworks including U.S. EPA Cleaner Technologies Substitutes Assessment,[8] BizNGO with GreenScreen,[9] and U.S. EPA Design for Environment Program.[7,78] Generally speaking, the quality of in silico data, at large, varies depending on, for example, experimental data used in training the models and their statistical performance[56] (see SI Section 6 for more details). Because of the identified data gaps in experimental data, the in silico data of the 20 criteria was used for the further decision-making process.

Decision Making Approaches. With data for 20 criteria, it is not trivial to identify a more or less hazardous decaBDE replacement, which emphasizes the need for a good decision



		decaBDE	DBDPE	EBTEBPI	TBBPA-BDBPE	TTBP-TAZ	BPBPE	EH-TBB	BEH-TEBP	4-PeBPOBDE208	BTBPE	DP	TTBNPP	TPHP	PBDPP	BPA-BDPP	TBEP	MA
P	Air half-life	🟥	🟨	🟩	🟩	🟧	🟩	🟩	🟩	🟥	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥
	Water half-life	🟥	🟥	🟥	🟥	🟥	🟥	🟧	🟧	🟥	🟥	🟥	🟥	🟨	🟨	🟧	🟨	🟨
	Soil half-life	🟥	🟥	🟥	🟥	🟥	🟥	🟨	🟨	🟥	🟥	🟥	🟥	🟨	🟨	🟨	🟨	🟨
	Sediment half-life	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥
	Biodegradation	🟥	🟥	🟥	🟥	🟥	🟥	🟧	🟧	🟥	🟥	🟥	🟥	🟨	🟨	🟧	🟨	🟨
B	BCF	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩
T	Mutagenicity	🟩	🟩	🟩	🟧	🟩	🟩	🟩	🟩	🟩	🟩	🟨	🟨	🟩	🟩	🟩	🟧	🟨
	Carcinogenicity	🟥	🟥	🟥	🟥	🟨	🟨	🟥	🟥	🟧	🟨	🟥	🟧	🟨	🟨	🟨	🟥	🟧
	Developmental toxicity	🟩	🟩	🟧	🟧	🟧	🟩	🟧	🟧	🟩	🟩	🟩	🟥	🟥	🟥	🟥	🟥	🟩
	Estrogen binding	🟨	🟨	🟨	🟧	🟨	🟩	🟩	🟨	🟨	🟨	🟨	🟨	🟧	🟧	🟨	🟩	🟩
	Androgen binding	🟧	🟧	🟧	🟧	🟧	🟧	🟧	🟨	🟧	🟧	🟥	🟧	🟩	🟧	🟧	🟩	🟩
	Transthyretin binding	🟩	🟩	🟩	🟥	🟩	🟩	🟩	🟩	🟥	🟩	🟥	🟩	🟩	🟩	🟩	🟩	🟩
	Skin sensitization	🟥	🟩	🟩	🟩	🟩	🟩	🟥	🟩	🟩	🟩	🟩	🟩	🟥	🟩	🟩	🟥	🟥
	Skin irritation	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟩	🟩
	Eye irritation	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟩	🟥	🟩	🟩	🟥	🟩
	Rat oral LD50	🟥	🟥	🟥	🟨	🟧	🟧	🟧	🟨	🟥	🟥	🟨	🟨	🟩	🟩	🟩	🟨	🟩
	Fish acute LC50	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟧	🟥	🟥	🟧	🟩
	Daphnia Magna LC50 48h	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟥	🟨
	T. pyriformis IGC50 48h	🟧	🟧	🟧	🟥	🟨	🟧	🟥	🟥	🟧	🟥	🟧	🟨	🟨	🟨	🟧	🟩	🟩
M	Mobility	🟨	🟩	🟧	🟨	🟩	🟨	🟧	🟨	🟩	🟧	🟨	🟧	🟥	🟧	🟨	🟥	🟥

Figure 2. Heat map of the 17 flame retardants where red indicates that a hazard criterion has been met, orange and yellow indicate high and moderate hazard level, and green indicates that the chemical has properties fulfilled a set safe level (SI Section 2). Thresholds for the four categories of each criterion is listed in SI Table S3.

strategy in alternatives assessment processes (SI Figure S10,). Here, three MCDA methods were tested.

Heat Map. The heat map (Figure 2), which color codes the ranges of each criterion, suggests that decaBDE is the most hazardous FR in the database as it has 10 of 20 categories (Table 1) labeled red, that is, classified as hazardous according to regulatory or literature cutoff values (SI Table S1); other substances have nine or fewer categories labeled red. Following this, six out of the other halogenated FRs obtained eight or nine red indicators (DBDPE, EBTEBPI, TBBPA-BDBPE, 4′-PeBPOBDE208, BTBPE, and DP), none of which are halogenated OPFRs. Among the five OPFRs, the brominated OPFRs TTBNPP and TBEP had seven red indicators, appearing more hazardous than the three nonhalogenated ones, TPHP, PBDPP, and BPA-BDPP, which had six, four, and five red indicators, respectively. Melamine had among the fewest red indicators, having only four, in addition to one orange, five yellow, and the highest number of green indicators (10). Melamine is often used together with OPFRs,[79,80] but has also been reported to have good flame retardancy itself.[81,82] PBDPP (four red, three orange, five yellow, and eight green indicators) appeared to be the best OPFR as well as the second best choice among all studied chemicals. The BFRs that appear as best alternatives are BEH-TEBP (five red, three orange, five yellow, and seven green indicators) and BPA-BDPP (five red, four orange, four yellow, and seven green indicators). All chemicals achieved at least one red indicator for P and T, though for M there was a scatter across all colors. The B property was flagged green for all chemicals, though it is known some of these substances bioaccumulate, such as decaBDE,[83,84] DP[85] and DBDPE.[55,56] In REACH, the B parameter is based on the estimated bioconcentration factor (BCF) in fish, with a limit value of 2000 for B^2. However, this does not account for other modes of bioaccumulation, for example, in soils or biomagnification through terrestrial food chains. In Europe decaBDE was classified as B because of similarities in fate to very bioaccumulative substances, and because transformation products of decaBDE are bioaccumulative substances.[83,84] DP also did not meet the BCF threshold, but has been classified as potential very bioaccumulative and should be handled as one[85] due to the frequent observations in aquatic biota, terrestrial organisms, and even humans. For DBDPE, this compound is very bioaccumulative, with a measured bioaccumulation factor (log BAF) up to 7.1,[55] considering food and diet, which is almost six log units higher than the log BCF value used in this study.[86,87] Thus, some flame retardants are clearly bioaccumulative, but their estimated BCF values are below 2000 which may be due to issues with the estimates or alternative uptake mechanisms, which points out the demand for using both experimental data and in silico data for assessing other B related measures like the biomagnification factor (BMF) or bioaccumulation factor (BAF). A previous review also pointed out that laboratory BCF data, which were commonly used for establishing BCF models, tend to be underestimated compared with field BAFs.[86] Unfortunately, such BAF measurements are lacking for model establishment.[86]

The heat map clearly shows that there is no clear winner among our target FRs, that none of the chemicals fully satisfies all the regulatory criteria (i.e., achieving no red indicators). These results agree well with a previous PBT screening of FRs including 14 substances of those studied here (except TBEP and melamine).[36] These authors concluded that the 14 FRs were either PB or PT, and three FRs (BPBPE, EH-TBB, and PBDPP) fulfilled their PBT criteria. This is a common situation in alternatives assessment for frameworks with fixed thresholds, such as the USEPA DfE[7] and GreenScreen,[9] that no sustainable choice is available and the demand has become to select the "least worst" choice. This means that the MCDA cannot be elegantly condensed into a "sorting problematic",[32] for example sorting chemicals into fully acceptable or fully unacceptable classes. Rather, a "ranking problematic" is called for, in which details like the relative half-lives are preserved and considered in conjunction with the other data. In such cases, a heat map has some disadvantages. First, since a different number of criteria are considered for each property, that is, 13 T criteria, 5 P criteria, and just 1 B and 1 M criterion, this allows T to arguably be overemphasized. Second, setting thresholds based on legislation or cutoff values from other alternatives assessment frameworks can make the differences between chemicals become less clear in the heat map for some criteria. For example, the sediment half-lives appear red for all 17 chemicals, that is, these chemicals all qualify for the very persistent criteria of REACH. Therefore, they all get the same color on the heat map despite the variation of almost a factor of 5 across all FRs.[7,9] Considering the discussion that B should be more than bioconcentration, adding further B criteria, such as bioaccumulation or biomagnification, will also make it more complex and difficult to identify the "least worse" option using a heat map; as the more criteria, the smaller the chance any of the alternatives will be hazard free.

MAUT. As a synthesizing criterion method, MAUT can manage the fact that P, B, M, and T have different numbers of criteria, by assigning weighing factors to all criteria to make P, B, T, and M equally important. Since the heat map indicates that using only legislative or literature values to determine cutoff values might not be suitable for our data, a new strategy was developed for MAUT, that for each criterion, input data on chemical hazards were scaled from 0 (worst) to 1 (best) based on the distance between our worst case to an ideal level, or a set worst case to our best case. Details for setting the scaling ranges are further presented in SI Section 7. The final scales for MAUT are listed in Table 3.

Consistent with the heat map, partial scores for the four properties (P, B, M, and T) from MAUT show that none of the FRs are good with respect to all properties (SI Figure S11). DecaBDE ranked worst for P and also had a poor T ranking. The best ranked FR according to the heat map, melamine, performed well on P, B, and T, but has the worst M ranking. The worst chemical with respect to T is TBBPA-BDBPE, and the worst with respect to B is BTBPE.

Though MAUT overcomes some of the limitations of using a heat map, by more clearly ranking substances, this method also has its own problems. First, MAUT requires aggregation independence,[87] which is problematic for diverse chemical hazard criteria, as some criteria may be correlated to similar physicochemical properties. For instance, the BCF and M factors correlate to some extent with K_{ow} for many substances. Toxicity through baseline narcosis is also directly related with K_{ow} for several nonpolar organics[88] including BFRs.[56] Another example is that half-lives for sediment, soil, and water calculated from EPISUITE are linearly correlated with each other. Second, the MAUT system illustrated here is based on average values and neglects the question of whether averages differ significantly, which may result in erroneous conclusions. One example is illustrated in SI Figure S12 where data from seven different models on acute toxicity (*Daphnia magna* LC50 48h) are compared and among the 17 case chemicals, only MA has a value that is significantly different from the others. MAUT therefore needs to be performed alongside a sensitivity analysis to see the robustness of conclusions.

ELECTRE III. ELECTRE III is an example of a synthesizing preference relational system that can use thresholds defined via

Table 3. Thresholds Settings for MAUT and ELECTRE III

MCDA method	MAUT		ELECTRE III		
assessment criteria	worst level (0)	best level (1)	indifference threshold (q)	preference threshold (p)	veto threshold (v)
half-lives	longest half-lives among case chemicals	an ideal best level (0 days)	0.25×(1 level in MAUT days-0 level in MAUT)	0.5×(1 level in MAUT days-0 level in MAUT)	0.75×(1 level in MAUT days-0 level in MAUT)
BCF	largest log BCF among case chemicals	an ideal best level (0)	minimum SD of different models among the chemicals	maximum SD of different models among the chemicals	0.75×(1 level in MAUT days-0 level in MAUT)
mobility (log K_{oc})	a set worst level (−2)	largest log K_{oc} value among target chemicals	minimum SD of different models among the chemicals	maximum SD of different models among the chemicals	0.75×(1 level in MAUT days-0 level in MAUT)
rat oral LD50	a set worst level (1 mg/kg)	largest LD50 value among target chemicals	minimum SD of different models among the chemicals	maximum SD of different models among the chemicals	0.75×(1 level in MAUT days-0 level in MAUT)
aquatic acute toxicity LC50s	a set worst level (1 ng/L)	largest LC50 values among target chemicals	minimum SD of different models among the chemicals	maximum SD of different models among the chemicals	0.75×(1 level in MAUT days-0 level in MAUT)
toxicity criteria with classification models	all model results estimated as positive	all model results estimated as negative	minimum SD of different models among the chemicals[a]	maximum SD of different models among the chemicals[a]	0.75×(1 level in MAUT days-0 level in MAUT)

[a] For transthyretin binding, skin sensitization, skin irritation, and eye irritation which only have one classification model for each criterion, we assumed that the model uncertainties were similar to the uncertainty of other classification models, thus *p* and *q* for these criteria were set to be equal to the maximum *p* and *q* of those human toxicity criteria with several classification models (mutagenicity, carcinogenicity, developmental toxicity, estrogen binding, and androgen binding).

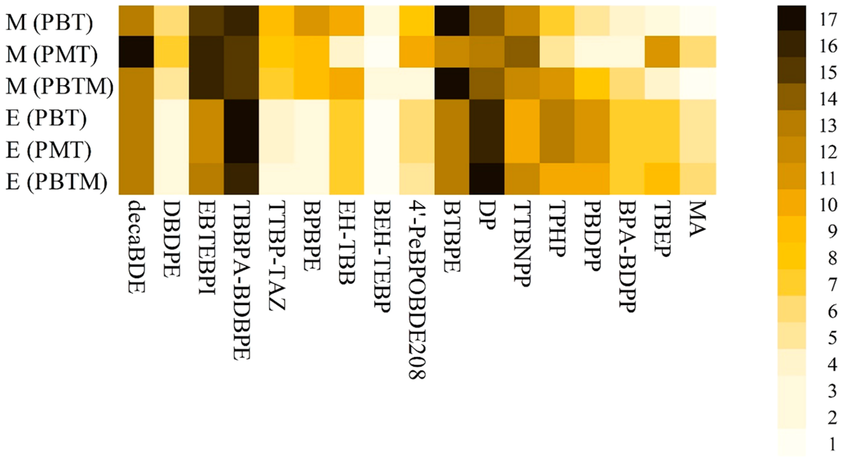


Figure 3. Different final score ranking results of the MAUT (M) and ELECTRE III (E) methods.

consideration of data uncertainties. There are three important thresholds for each criterion in ELECTRE III: indifference thresholds (q), preference thresholds (p), and veto thresholds (v). In practical terms, when the difference between alternatives A and B with respect to criterion j is less than q, the weight of criterion j is not considered in the comparison between A and B, and if the difference is larger than p, the full weight of criterion j should be awarded to the superior alternative. A sliding scale exists between p and q, but if the difference is as large as a defined v, the ELECTRE method eliminates the underperforming alternative from contention.[34,73] In this study, q and p were set based on data uncertainties by considering standard deviation (SD) of different model results for the same criteria for each of the chemicals. Details regarding the settings for q, p, and v is shown in Table 3.

The partial scores of B and M are identical between ELECTRE III and MAUT, since each property is based on only one criterion (SI Figure S13). With the consideration of data uncertainties, the P score for several chemicals were indifferent compared with each other by ELECTRE III (for example seven of the chemicals were ranked one and eight were ranked eight). The ranking of T is generally similar between MAUT and ELECTRE III, but for a few chemicals it differed considerably. For example, TBEP was ranked the second worst (16) by MAUT but average (10) by ELECTRE III.

Final Score Approaches. Figure 3 presents different final score approaches by both MAUT and ELECTRE III, compounding the end points PBT, PMT, and PBMT. The two different MCDA methods generally reach similar ranking (SI Figure S14), where EBPEBPI, TBBPA-BDBPE, BTBPE, and DP were ranked poorly together with decaBDE for all strategies (PBT, PMT, and PBMT) under both methods, indicating potential regrettable substitutions, whereas DBDPE, BEH-TEBP, and melamine are relatively better alternatives. However, these three compounds also have their problems. [55]DBDPE is bioaccumulative as discussed above, with reported log BAF (6.1−7.1) an order of magnitude higher than decaBDE in fish.[55,56] Another consideration is transformation products. For BEH-TEBP, although it generally ranked best in our assessment, studies have shown that one of its transformation products is more toxic, viz., mono(2-ethyhexyl) tetrabromophthalate (TBMEHP).[89] TBMEHP was studied in all our models and the results indicate only one extra red flag in the heat map than BEH-TEBP, whereas the ranking in MAUT (PBMT) decreased from second to sixth position. A large range of biotic and abiotic transformation products could theoretically be generated from studied FRs and as an example the OECD QSAR Toolbox generated 12−90 different transformation products for the studied FRs. However, an important consideration is yields of some of these transformation products may be only formed in minor or negligible quantities. But the issue of yields also relates to mass, and therefore, differences in tonnages required across FRs, when used in products for achieving a similar effect for the decaBDE it is replacing. Assessing transformation products, their yields, and tonnage/exposure considerations warrants further development for inclusion in a more quantitative and comprehensive alternatives assessment procedure than presented here. For melamine, it generally appears to be a less toxic compound with no hazardous transformation products, whereas all MCDA methods suggested that it is a potential PM compound. This compound has been heavily used in many applications besides as a flame retardant and thus environmental and human exposure may be a lot higher than other alternatives, which would need further evaluation via quantitative risk assessment. All the five OPFRs included in this study ranked better than decaBDE, but on the other hand, they were not generally ranked better than the BFRs.

The two different MCDA methods yielded also some different results. For example, the PBMT ranking in MAUT for BPBPE is nine, whereas the same approach in ELECTRE III ranked it three. The major reason for the ranking differences besides the fundamental difference between the two MCDA methods is that none of our case chemicals is worse than any other case chemicals for all properties (except for the case of DBDPE, which is no worse than decaBDE for all 17 properties), a situation which facilitates rank reversal. Generally, the inclusion of M as a hazard property had a low impact on ranking of the studied chemicals except if using MAUT and in particular for OPFRs, where four out of five compounds were ranked worse if applying PBMT as compared with PBT. The compound most affected by the inclusion of M was 4′-PeBPOBDE208, for which ranking improved from eight to three based on low mobility.

Environmental Implications. Exchanging chemicals in materials and products with safer alternatives can be a tedious and costly process; available methodologies require interdisciplinary approaches, broad competences, and lots of data. In silico methodologies can provide a means to fill data gaps and speed up processes. Good decision making requires strategies and methodologies that consider uncertainties in data and the multitude of aspects including environmental, consumer, and occupational hazards; in addition to data on the chemical's product effectiveness, life cycle, and economic factors. Different MCDA methods have their own advantages and disadvantages. Here we assessed a range of alternatives to decaBDE using mainly in silico based data with a focus on environmental and human health hazards. The absence of a fully compliant, clear "winner" was indicated by the heat mapping which instead showed the value of continuing the search for sustainable decaBDE alternatives. Inorganic FRs and polymer FRs were excluded from this study due to their unsuitableness to the applied in silico methodologies but could potentially provide more sustainable options. Alternative approaches including rule-based protocols have been suggested both for inorganics[90] and polymers,[91,92] which could be included in future assessments. However, when alternative options are limited, it is not always a question of picking a compliant chemical, but the "least worst" alternative. In this study, we use two MCDA methods (MAUT and ELECTRE III) to achieve this, and were able to incorporate more subtleties in the underlying data. For the identified "less hazardous" chemicals, more detailed hazard assessment should be conducted including their possible transformation products, yield, and other criteria like technical feasibility and tonnage produced. We also noted that inclusion of the M can reduce the risk of underestimating hazards of more hydrophilic compounds (e.g., OPFRs). It is an unfortunate reality that uncertainties for both experimental and in silico data are generally large. In the future, besides the demand for high quality data or models, we recommend that MCDA methods like ELECTRE III be implemented with consideration of not only the regulatory thresholds, but also data uncertainties. Since our approach focused on the hazard criteria, for any possible better alternatives identified, a quantitative risk assessment with a more thorough exposure assessment might need to be carried out, since the emissions and exposures can vary due to different use patterns and physicochemical properties. For flame retardants used in several consumer products, indoor exposure is of particular concern for humans. It also has to be acknowledged that important chemical hazards are overlooked, such as BAF and BMF. In principle, the combination of in silico tools and MCDA methods could be expanded to explore these additional properties; further, the quantitate exposure aspects could be adjusted by considering different use and emission levels. It is unlikely that there will be enough empirical data to compare these diverse considerations; however, the combination of in silico tools and MCDA methods could also be developed for the broader selection of alternative substances and how they ought to be used.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.8b07163.

> Detailed information on the chemical database establishment; threshold settings for heat mapping; chemical variation results analyzed by PCA; data gaps and data comparability issues of experimental data collected from the ECHA database of the REACH dossiers; how the data gaps of in silico data were filled; data quality of the calculated in silico data; data pretreatment and thresholds determination for MAUT and ELECTRE III (PDF)
>
> Collected experimental and in silico data; MAUT and ELECTRE III calculation sheets (XLSX)

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Notes

The authors declare no competing financial interest.

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