EPA Public Access

Author manuscript

Clean Technol Environ Policy. Author manuscript; available in PMC 2018 May 01.

About author manuscripts

Submit a manuscript

Published in final edited form as:

Clean Technol Environ Policy. 2017 May 1; 19(4): 1067–1086. doi:10.1007/s10098-016-1300-2.

A framework for an alternatives assessment dashboard for evaluating chemical alternatives applied to flame retardants for electronic applications

Todd M. Martin^{*,1}

^{*}National Risk Management Research Laboratory, U.S. Environmental Protection Agency, 26 W. Martin Luther King Dr., Cincinnati, OH, 45268, USA

Abstract

The goal of alternatives assessment (AA) is to facilitate a comparison of alternatives to a chemical of concern, resulting in the identification of safer alternatives. A two stage methodology for comparing chemical alternatives was developed. In the first stage, alternatives are compared using a variety of human health effects, ecotoxicity, and physicochemical properties. Hazard profiles are completed using a variety of online sources and quantitative structure activity relationship models. In the second stage, alternatives are evaluated utilizing an exposure/risk assessment over the entire life cycle. Exposure values are calculated using screening-level near-field and far-field exposure models. The second stage allows one to more accurately compare potential exposure to each alternative and consider additional factors that may not be obvious from separate binned persistence, bioaccumulation, and toxicity scores. The methodology was utilized to compare phosphate-based alternatives for decabromodiphenyl ether (decaBDE) in electronics applications.

Keywords

Alternatives assessment; Human toxicity; Ecotoxicity; Exposure; Life cycle impact assessment

1. Introduction

The goal of alternatives assessment (AA) is to facilitate a comparison of the advantages and disadvantages of alternatives to a chemical of concern, resulting in the identification of safer alternatives (National Research Council 2014). Alternative assessment frameworks usually include an assessment of human health and ecological hazards. Assessment of human health hazards evaluate an array of human health endpoints including carcinogenicity, mutagenicity, reproductive and developmental toxicity, endocrine disruption, dermal and eye irritation, and others (National Research Council 2014). It is important to consider a wide array of toxicity endpoints in order to avoid regrettable substitutions, as in the case where methylene chloride was replaced by n-hexane for automotive applications (n-hexane was

¹Author to whom correspondence should be addressed: Telephone: (513)-569-7682; Fax: (513)-569-7677; martin.todd@epa.gov.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.

later found to cause peripheral neuropathy) (Wilson et al. 2007). Typically AA frameworks utilize criteria tied to global harmonization scores (GHS) (UNECE 2007) to classify chemicals in terms of toxicity. However, most chemicals have not been assigned hazard and risk scores for a majority of the important toxicity endpoints. It is recommended that novel high throughput and *in silico* approaches be utilized to fill the many data gaps (National Research Council 2014).

Most AA frameworks assume that the different chemical alternatives for a given application have similar exposure characteristics (National Research Council 2014). Alternatively, one can use available exposure models or utilize physicochemical properties to estimate relative exposure. Physicochemical properties can be used to determine which environmental compartment the chemicals will partition into, estimate the potential for bioconcentration and bioavailability, and estimate the likelihood of mammalian or aquatic exposure.

Recognizing the critical need for exposure-based prioritization approaches on par with those for toxicity, the U.S. Environmental Protection Agency (US EPA) has initiated the ExpoCast program (Cohen Hubal et al. 2010) to better evaluate and prioritize chemicals based on biologically relevant human exposures. Current research seeks robust approaches that use human exposure data, product use information, and modeled human behavior to systematically prioritize potential for exposure, based on chemical properties, product life cycle, and individual and population characteristics (Cohen Hubal et al. 2010). To be most useful, approaches (tools, schemes or models) for prioritizing chemicals based on exposure should consider potential for exposure across the full life cycle of chemical substances and should address both near-field (from consumer products) and far-field (from the greater environment) exposure. Egeghy and coworkers reviewed many different exposure prioritization approaches including EUSES (Vermeire et al. 2005), USETox (Rosenbaum et al. 2011), and RAIDAR (Arnot et al. 2006).

A life cycle impact assessment (LCIA) is a quantitative evaluation of potential human health, environmental, and social impacts of the material and energy flows (resources acquired from the environment and releases to the environment) identified during the Life Cycle Inventory (National Research Council 2014). By quantifying the potential for impact in a variety of categories, including global climate change, ozone depletion, acidification, eutrophication, smog formation, land use, water use, mineral and fossil fuel uses, LCIA attempts to avoid shifting environmental impacts to other impact categories without understanding the consequences of more narrowly defined decision frameworks. Most life cycle inventories include four major stages: (1) Raw material extraction; (2) Chemical manufacture; (3) Product manufacture (electronics, textiles); (4) End of life (recycling, incineration, and landfill). In order to increase the comprehensiveness of the evaluation, risk from chemical emissions for the alternatives should be evaluated by considering exposure from emissions during all stages.

In this study, a comprehensive alternatives assessment (AA) methodology based on the National Research Council (NRC) framework document (National Research Council 2014) will be presented. The methodology will be utilized to create web-based dashboard for

evaluating chemical alternatives. The scope of the methodology will encompass the following steps in the NRC framework:

- Step 5 Assess physicochemical properties
- Step 6.1 Assess Human Health Hazards
- Step 6.2 Assess Ecotoxicity
- Step 6.3 Conduct comparative exposure assessment
- Step 7. Integration of information to Identify Safer Alternatives
- Step 8. Life cycle thinking

Empirical and predicted data indicate that brominated flame retardants such as decabromodiphenyl ether (decaBDE) are highly persistent in the environment and have been found in high and increasing concentrations in the sediment of lakes, rivers, streams and estuaries (Environment Canada 2006). Additionally, they have been measured in ambient atmospheric particulates (Illinois Environmental Protection Agency 2006) and in the Arctic environment, providing evidence that they are subject to long-range transport (Environment Canada 2006). In addition flame retardants and pesticides have been detected in infant cord blood (although many other chemicals are detected in cord blood as well) (Fukata et al. 2005). Most commercially available chemicals are not monitored in environmental media, and thus their potential for human exposure are unknown. Under the modernized Toxic Substances Control Act (TSCA) (US EPA 2016e), EPA relies on surrogates including chemical release, product formulation, use category, physical and chemical properties, and estimates of persistence and bioaccumulation potential to evaluate exposure potential.

As an example, this AA methodology will be utilized to aid in evaluating alternatives for decaBDE. The main use of decaBDE was in the front and back panels of televisions made of high impact polystyrene (US EPA 2014a). DecaBDE has been used at high volume (releases in 2002 totaled ~1.25 million pounds to air, water and land (US EPA 2016g)) in a broad range of products, but is now being phased out in the U.S. and in Europe (Wikipedia.org 2016). The most cost-effective non-halogenated substitutes for decaBDE involve changing the resin system and the use of phosphorous-based flame retardants (The Lowell Center for Sustainable Production 2005). Flame retardants are designed to be stable at high temperatures and thus they typically degrade slowly in the environment (i.e. they are persistent) and sometimes have high ecotoxicity (The Lowell Center for Sustainable Production 2005). Certain brominated flame retardants are particularly persistent and toxic and therefore should be replaced (Chen and Hale 2010; D'Silva et al. 2004). Alternative flame retardants must not only have a favorable environmental profile, but must provide satisfactory (or superior) fire safety, have an acceptable cost, and attain the appropriate balance of properties (e.g., mechanical, thermal, aesthetic) in the final product (US EPA 2014a). In this study, we considered the non-halogenated phosphate-based alternatives for decaBDE, which were evaluated in a Design for the Environment (DfE) study (US EPA 2014a) and a GreenScreen study (Clean Production Action 2007).

2. Methods

2.1. Overview of alternatives assessment methodology

This AA methodology involves two major stages. In the first stage, steps 5, 6.1, 6.2, and 7 of the NRC framework (National Research Council 2014) are included and a hazard profile in terms of human toxicity, ecotoxicity, and physicochemical properties, is generated for each alternative (see Figure 1). In the second stage, the best alternatives (determined from expert judgement of the tradeoffs in the hazard profiles) are evaluated in terms of exposure (and risk) over the entire product life cycle (see Figure 2). The second stage involves steps 6.3 and 8 of NRC framework and involves evaluation of the exposure and risk from chemical emissions throughout the product life cycle. Emissions are considered from both near-field and far-field sources. Detailed exposure calculations should only be performed for alternatives which have been found to have a superior hazard profile when compared to the chemical of concern. If the alternatives are expected to have substantially equivalent exposure, then the comparison can be mainly hazard based (i.e. stage 1 is sufficient). If an alternative is deemed to have a substantially higher potential for exposure than the chemical of concern, then a more detailed exposure assessment may be appropriate.

2.2. Physicochemical properties

Physicochemical properties are useful for determining the environmental fate of a chemical and help determine which exposure pathways are relevant (see Table 1). For example, the melting point and boiling point can be utilized to determine the state of matter (solid, liquid, or gas) for a given ambient temperature (T_{ambient}). Chemicals with a low melting point also have a higher potential to be absorbed through the skin, gastrointestinal tract, and lungs (US EPA 2014a). Chemicals which have high vapor pressures are much more likely to be inhaled and those with a low flash point are dangerous because they are flammable.

Chemicals with higher water solubility are more likely to be transported into surface water with runoff during storm events and into groundwater by infiltrating through the unsaturated soil zone. In addition they are more likely to be absorbed through the gastrointestinal tract or lungs, partition to aquatic compartments, undergo atmospheric removal by rain washout, and possess a greater potential for human exposure through the ingestion of contaminated drinking water. Whereas, chemicals with lower water solubility are generally more persistent and have a greater potential to bioconcentrate (US EPA 2014a). If an aquatic toxicity is estimated to occur at a concentration higher than the water solubility, the adverse effect cannot be reached thus indicating low potential harm from aquatic toxicity.

$\log K_{OW}$ is frequently used as a surrogate for water solubility, if an experimental value is not available. $\log K_{OW}$ can also be used to estimate other properties important to the assessment, including bioconcentration and soil adsorption, and is a required input for SAR models used to estimate ecotoxicity values. $\log K_{OW}$ is also used to estimate $\log K_{OA}$ (log of the octanol – air partition coefficient) which is an important chemical property for estimating near-field exposure (Weschler and Nazaroff 2010).

In this AA methodology, in the absence of experimental data, persistence will be evaluated using the half-life in the predominant environmental compartment (e.g. air, water, soil, or

sediment). The predominant compartment receives the highest fraction of the chemical according to the level III fugacity model included in Estimation Program Interface Suite (EPISUITE) (Mackay 1991; Mackay et al. 1996a; Mackay et al. 1996b; US EPA 2012). This model assumes equal emissions of the chemical to air, water, and soil. The persistence score will be assigned using the DfE (Office of Pollution Prevention & Toxics 2011) classification scheme (see Table 1). If available, results from experimental biodegradation tests (such as the percent of theoretical ultimate degradation in the Ready Biodegradability test (OECD 1992)) can be used to assign the persistence class (US EPA 2014a).

Biodegradation processes are divided into two types. The first is primary biodegradation, in which a chemical substance is converted into another substance. The second is ultimate biodegradation, in which a chemical is completely mineralized to small building-block components (e.g., carbon dioxide and water). Chemical substances that undergo rapid primary degradation, but only slow ultimate biodegradation are considered to have stable metabolites (US EPA 2014a). Possible metabolites can be generated using US EPA's Chemical Transformation Simulator (CTS) (Wolfe et al. 2016) which generates two sets of possible metabolites: abiotic (such as in surface water) and metabolic (due to human metabolism). DfE criteria utilize ultimate biodegradation preferentially for the persistence hazard designation, although primary removal rates are informative in assigning hazard designations particularly for materials that are transformed slowly, and to a lesser extent for those that are transformed rapidly (US EPA 2014a).

Bioaccumulation is a process in which a chemical is absorbed by an organism via all routes of exposure (i.e. from dietary and ambient environmental sources). Bioaccumulation is characterized by the bioaccumulation factor (BAF), the steady state ratio of a chemical in an organism relative to its concentration to the ambient environment. Because experimental BAFs are not commonly available, the bioconcentration factor (BCF) is typically used to evaluate the hazard due to bioaccumulation. The BCF is defined as the ratio of the concentration of a chemical in an organism (typically fish) to the concentration in the organism's surroundings (i.e. water). BCF values can be obtained from experimental values or predicted using software such as EPISUITE (US EPA 2012) or EPA's Toxicity Estimation Software Tool (T.E.S.T.) (US EPA 2016f). T.E.S.T. can also estimate physicochemical properties including melting point, boiling point, vapor pressure, flash point, and water solubility.

2.3. Human Health Hazards

The NRC framework document (National Research Council 2014) recommends including the following human health hazards for comparing chemical alternatives: acute toxicity, carcinogenicity, mutagenicity, reproductive toxicity, developmental toxicity, respiratory sensitization/irritation, neurotoxicity, endocrine activity, skin sensitization, and skin and eye corrosion/irritation. In this alternatives assessment dashboard, it is proposed all these endpoints be included. Values for each of these endpoints will be provided using a combination of experimental data, predictions from quantitative structure activity relationship (QSAR) models such as in T.E.S.T. and values obtained from Global Harmonization System (GHS) scores.

In the NRC framework document (National Research Council 2014), it is also recommended *in vitro* data be used as much as possible to reduce data gaps. *In vitro* scores typically cannot be used for risk assessment decisions unless they are converted to *in vivo* dose equivalents. High throughput screening data do not account for pharmacokinetic factors and may not account for metabolism (National Research Council 2014); therefore, *in vivo* data are strongly preferred for most toxicity endpoints. However, *in vitro* data can be utilized as primary endpoints such as mutagenicity and skin sensitization. Recently, hierarchical clustering models were developed for *in vitro* estrogen receptor (ER) endpoints (binding, agonism, and antagonism) and for *in vivo* ER binding (Martin 2016). It has been observed that models fit to *in vitro* assay scores may not produce superior results for prediction of *in vivo* toxicity endpoints than those models which are based solely on molecular descriptors (Thomas et al. 2012). However, it was observed that adding predicted *in vitro* scores to the available variable pool improved the prediction accuracy of *in vivo* ER activity models (Martin 2016).

2.4. Ecotoxicity

The NRC framework document (National Research Council 2014) recommends generating ecotoxicity comparisons for the species which are exposed to the highest intake rate of the chemicals of interest. Due to lack of data, ecotoxicity will have to be evaluated in terms of acute and chronic aquatic and rodent toxicity. Aquatic toxicity will be evaluated using models and experimental data for common species (such as fathead minnow). Rodent toxicity will be evaluated using models and data for rodents, such as rats and mice.

2.5. Generation of hazard profile scores

A hazard profile consists of scores (low, medium, high, and very high) in human health hazards, ecotoxicity, and fate. In order to generate a complete profile, scores need to be obtained from a variety of sources. Ideally scores are obtained from GHS data from curated public databases such as the Classification and Labeling (C&L) Database (European Chemicals Agency 2016), ACToR (US EPA 2016a), IRIS (US EPA 2016c), IARC (International Agency for Research on Cancer (IARC) 2016), HSDB (U.S. National Library of Medicine 2016), NITE (National Institute of Technology and Evaluation (NITE) 2016), ECOTOX (US EPA 2016b), ChemHat (Chemhat.org 2016), and the advisory list for self-classification of dangerous substances (Danish Ministry of the Environment's Environmental Protection Agency). Pharos (Pharos 2016) is an excellent resource for hazard scores from multiple databases, but it is only available via a subscription. Additionally, ChemHat and ACToR provide scores from multiple sources.

In our AA methodology, binning of toxicity values into scores (i.e. very high, high, moderate etc.) will be based on the DfE scoring system (US EPA 2011a). For example, scores from different sources are converted into DfE mammalian toxicity scores, as shown in Figure 3. The older EU risk phrases (European Commission 2008) do not overlap perfectly with the DfE scoring system for some endpoints, so they are not a preferred source (unless the quantitative toxicity value is available elsewhere). The European Union Classification, Labeling and Packaging (EU CLP) scores (European Union 2008) and DfE scores (US EPA

2011a) overlap with the GHS categories (UNECE 2007) with the exception of those very high DfE scores where GHS categories 1 and 2 are combined.

Manually culling hazard endpoint data to generate a complete hazard profile takes approximately eight hours (Wehage et al. 2016). Therefore the time required for data collection is a barrier for implementation of most alternative assessment methodologies such as the GreenScreen (Clean Production Action 2007). Wehage et al (Wehage et al. 2016) developed an automated system to download GHS data from Japan's National Institute of Technology and Evaluation (NITE) website. In order for the AA methodology outlined in this paper to be successful, data will need to be mined from a wide variety of freely available websites in order to minimize data gaps and facilitate AA usability.

For chemicals with data gaps, toxicity values and physicochemical properties can be estimated using QSAR models such as T.E.S.T. which estimates toxicity endpoints and physical properties utilizing QSAR methodologies such as hierarchical clustering, multilinear regression, nearest neighbor, and consensus approaches (US EPA 2016f). For human health hazard, currently T.E.S.T. can provide estimates for acute mammalian toxicity (oral rat LD₅₀), developmental toxicity (yes/no binary prediction), and mutagenicity (Ames mutagenicity). ER activity and skin sensitization are to be added to a future release of T.E.S.T. Respiratory sensitization is an important endpoint, but there are no widely accepted models for this endpoint (National Research Council 2014). Development of models for chronic toxicity is difficult due to the small size of most data sets and that different toxic effects can occur at low doses over a long period. T.E.S.T. can provide estimates for ecotoxicity in terms of acute aquatic toxicity (96 hour fathead minnow LC₅₀, 48 hour *Daphnia magna* LC₅₀, and 48 hour *Tetrahymena pyriformis* IGC₅₀) and acute mammalian toxicity (oral rat LD₅₀).

T.E.S.T.'s hierarchical clustering method was found to yield the highest accuracy of any single method, but the consensus approach (a straight average from all available methods) was found to give a slight increase in prediction accuracy and coverage (fraction of chemicals which can be predicted). The nearest neighbor approach is essentially an analog-based approach, since the predicted value is the average of three most similar chemicals in the training set. The nearest neighbor method (Martin et al. 2008) will be utilized in the AA methodology to identify and select analogs with available toxicity scores to fill in data gaps for endpoints which cannot be estimated using QSAR methods. This will enable users to select analogs with available GHS values for toxicity/ecotoxicity categories to obtain a more complete hazard profile. T.E.S.T. will be directly incorporated into this AA dashboard to allow rapid and convenient display of toxicity and physical property values.

CTS (Wolfe et al. 2016) will also be incorporated into this AA dashboard via web-services. CTS can calculate the following properties: melting point, boiling point, water solubility, vapor pressure, molecular diffusivity, ionization constant, pKa, Henry's Law Constant, and octanol/water partition coefficient. These properties are predicted using EPISUITE (US EPA 2012) and ChemAxon models (ChemAxon). CTS will be utilized to generate metabolites for each alternative. The hazard profile of each metabolite will also be evaluated for a more comprehensive evaluation of the alternatives.

Researchers at the Technical University of Denmark (Niemelä et al. 2010) have compiled QSAR predictions for mutagenicity, carcinogenicity, reproductive toxicity, acute oral toxicity, skin irritation, skin sensitization, and danger to the aquatic environment for 33,835 chemicals. In the future, similar toxicity models will need to be incorporated into this AA dashboard.

Once the hazard profile (physicochemical properties, human health hazards, and ecotoxicity) is complete for all the chemical alternatives and their metabolites, risk assessors can weigh the pros and cons of each alternative. The physicochemical properties can provide an indication as to which human health hazards and ecotoxicity are the most relevant for comparing alternatives. In addition, the exposure assessment (stage 2) can provide a more quantitative evaluation of which categories are the most important. For example, exposure assessment might reveal the largest risk is from inhalation from near-field sources or it might indicate ecotoxicity is the most important due to high water concentrations relative to aquatic toxicity values. Approaches such as GreenScreen (Clean Production Action 2007) aggregate toxicity information by determining a composite score. While such an approach may be easy to use, it obscures information that should be considered across domains (National Research Council 2014).

2.6. Far-field exposure

While reducing risk is the fundamental objective, for practical reasons most current methods first screen for hazards (persistence (P), bioaccumulation (B), and toxicity (T) properties) followed by exposure and risk assessment (Arnot and Mackay 2008). The problem with this approach is there is a subjective judgement about the relative importance of P, B, and T. In addition, it may erroneously include chemicals which pose little risk due to the low quantities emitted (false positive) or exclude high volume chemicals which are relatively nonhazardous (false negative). Finally, hazard ranking typically employs arbitrary cutoff defined values, which can yield difficulties when comparing chemicals with values near the cutoff values. The ultimate regulatory goal is to control risk rather than hazard (Arnot et al. 2006).

The lack of monitoring data for most commercial chemicals necessitates the use of models which can predict fate and transport and exposure. The source-to-human exposure relationship is a function of the substance's mode of entry to the environment (air, water, soil), fate (intermedia transport, degradation) and food web bioaccumulation processes (bioconcentration, biomagnification, biotransformation), and all significant human multimedia intake rates (inhalation and ingestion).

Arnot and Mackay developed a method based on the Risk Assessment IDentification, And Ranking (RAIDAR) multimedia model (Arnot et al. 2006) to evaluate chemicals using P, B, T, and Q (quantity) simultaneously in a continuous manner (i.e. no cutoff values) (Arnot and Mackay 2008). Models such as RAIDAR are designed to assess far-field impact of chemical exposure and does not include near-field sources such as indoor or product use to account for exposure to humans in domestic and industrial settings. RAIDAR utilizes level II or level III steady-state models to calculate concentrations in the bulk compartments (air, water, soil, and sediment) of a regional scale (100,000 km²) environment (Arnot et al. 2012). RAIDAR

and the European Union System for the Evaluation of Substances (EUSES) (Vermeire et al. 1997) were shown to be in general agreement, which is expected since the fate and transport calculations are conceptually similar (Arnot et al. 2010). Using the RAIDAR multimedia model, estimates of exposure potential using human concentrations and a unit emission rate span approximately 13 orders of magnitude, and intake fractions spanning 7 orders of magnitude (Arnot et al. 2012). The priority setting resulting from traditional cut-off based methods were largely inconsistent with the multimedia partitioning based method developed by Arnot and Mackay (2008). It has been shown that biotransformation in the organism and its food web is a more significant determination of bioaccumulation than partitioning properties (such as $\log K_{OW}$ and $\log K_{OA}$) (McLachlan et al. 2011). Thus, high-throughput, screening-level multimedia exposure models, such as RAIDAR, may be helpful to more accurately assess the extent of bioaccumulation for a given chemical.

Wambaugh et al. (Wambaugh et al. 2013) developed empirical models for environmental concentrations using far-field mass balance models (USETox (Rosenbaum et al. 2011) and RAIDAR) as an indicator for indoor and/or consumer use. Information on use was found to be the most predictive in correlated measured exposure data from NHANES (Wambaugh et al. 2013). In general, chemicals identified above the detection limit had consumer/indoor use. Wambaugh and coworkers (Wambaugh et al. 2014) developed regression models to fit NHANES exposure data using production volume, chemical use categories, and physicochemical properties as independent variables. Utilizing two or more descriptors described about 50% of the variance ($R^2 \sim 0.5$), which is a significant improvement of previous models based on far-field models ($R^2 \sim 0.15$). Half-lives in environmental media and the BCF most distinguished one compound from another. The research of Wambaugh and coworkers illustrates the need to consider near-field emissions and chemical use in addition to far-field sources in order to accurately estimate exposure and thus risk. In fact, models such as USETox are being modified to include indoor inhalation in industrial and home settings (Rosenbaum et al. 2011).

Level III models require mode of entry information specifying the total unit emissions to each bulk compartment. Several options exist for specifying the fraction emitted to each compartment:

- Assume equal fractions to air, water, and soil
- Utilize tabular European Union Technical Guidance emission factors (European Commission 2003) based on vapor pressure and water solubility. Utilizing these factors, the fractions released to air, water, and soil for typical brominated flame retardants are 0.004, 0.11, 0.0092, respectively
- Wambaugh et al (Wambaugh et al. 2013) assumed pesticide emissions were 50% to air and 50% to soil and all other chemicals were assumed to be emitted 80% to water, 10% to soil, and 10% to air

However, it was shown that relative risk rankings were generally robust to mode of entry scenarios for the RAIDAR model (Arnot and Mackay 2008).

2.7. Near-field exposure

The US EPA is developing a strategy for high-throughput (HT) exposure-based prioritization of chemicals under the ExpoCast program (Cohen Hubal et al. 2010). These novel modeling approaches allow one to evaluate chemicals based on their potential for biologically relevant human exposures. Thus they aid in determining which chemicals need additional toxicity testing and prioritization for chemical risk assessment.

The Stochastic Human Exposure and Dose Simulation Model for Multimedia, Multipathway Chemicals High-throughput (SHEDS-HT) model is a simplified version of the Stochastic Human Exposure and Dose Simulation Model for Multimedia, Multipathway Chemicals (SHEDS-MM) model (Isaacs et al. 2014). In modeling indirect exposures from near-field sources, SHEDS-HT employs a fugacity-based module to estimate concentrations in indoor environmental media. These concentration estimates, along with relevant exposure factors and human activity data, are then used by the model to rapidly generate probabilistic population distributions of near-field indirect exposures via dermal, non-dietary ingestion, and inhalation pathways (Isaacs et al. 2014). Population dietary exposures for a variety of chemicals found in foods are combined with the corresponding chemical specific near-field exposure predictions to produce aggregate population exposure estimates. SHEDS-HT successfully reproduced the pathway-specific exposure results of the higher-tier SHEDS-MM for a case-study pesticide and produced median intake doses significantly correlated ($p < 0.0001$, $R^2 = 0.39$) with medians inferred using biomonitoring data for 39 chemicals from the National Health and Nutrition Examination Survey (NHANES) (Wambaugh et al. 2013). Models such as SHEDS-HT that simulate exposure through dermal, non-dietary ingestion, and inhalation pathways are applicable to consumer products and pesticides, but may not be applicable to the case of flame retardants used in the plastic backing of television screens. However, Shin et al. assumed 10% of the compounds that are introduced to the home as part of a solid product would be released into the air for their near-field exposure model calculations (Shin et al. 2015).

2.8. Assessment of hazard and risk

Chemical risk can be evaluated in terms of ratios involving chemical concentrations, intake rates, or intake fractions. Arnot et al. assessed risk in terms of the risk assessment factor (RAF) (Arnot and Mackay 2008):

$$RAF = (C_U / C_T) (E_A / E_U) = C_A / C_T \quad (1)$$

where C_U = calculated concentration in the representative organisms in mol/m^3 for a unit emission rate, C_T = whole body concentration that represents a threshold (toxic) effect in mol/m^3 , E_A = actual emission rate in mol/hr , E_U = unit emission rate (i.e. 1 mol/hr), and C_A = actual concentration in mol/m^3 . A relatively high RAF indicates the need for further assessment, but some substances with low RAF may require more detailed considerations especially if the emissions are localized (i.e., near-field models are required) (Arnot et al. 2006). In the absence of emission data, chemicals can be compared in terms of the hazard assessment factor (HAF) (Arnot and Mackay 2008):

$$\text{HAF} = C_U / C_T \quad (2)$$

The RAF and HAF ratios can be calculated for different species, and the largest ratio identifies the species subject to the greatest hazard. It was also found that the inclusion of quantity (i.e. RAF vs HAF) significantly altered the rankings for chemicals evaluated (Arnot and Mackay (2008)).

Alternatively, chemicals can be evaluated in terms of a bioactivity quotient (BQ) (Shin et al. 2015). Bioactivity quotients are conceptually similar to other exposure/effects metrics, such as the RAF. The BQ is calculated as follows:

$$\text{BQ} = iR / \text{OED} \quad (3)$$

where iR = intake rate in mg/kg/day and OED = oral equivalent dose in mg/kg/day. Shin and coworkers (Shin et al. 2015) estimated the OED using *in vitro* toxicity data:

$$\text{OED} [\text{mg/kg/day}] = \text{ToxCast } AC_{50} \text{ or } \text{LEC} [\mu\text{M}] / C_{ss} [\mu\text{M}] \times 1 [\text{mg/kg/day}] \quad (4)$$

where C_{ss} = steady state chemical blood concentration estimated using *in vitro* to *in vivo* extrapolation (IVIVE) (Wetmore et al. 2015). The AC_{50} value used is the smallest value from all of the active assay results and thus is a conservative estimate of toxicity since not every assay is directly indicative of a toxic or negative effect. In addition, it has been shown there are some difficulties in using *in vitro* assays to predict *in vivo* toxicity (Martin et al. 2011; Thomas et al. 2012).

In a third approach, Rosenbaum et al. (Rosenbaum et al. 2011) evaluated hazard in terms of the ED_{50} (the effect (or toxic) dose that results in a toxic effect to 50% of the exposed population for a lifetime exposure). ED_{50} values were found to be correlated with oral rat lethal LD_{50} values:

$$\text{Chronic cancer } ED_{50} = LD_{50} / 129 \quad (R^2 = 0.32) \quad (5)$$

$$\text{Chronic non- cancer } ED_{50} = LD_{50} / 26 \quad (R^2 = 0.45) \quad (6)$$

Because LD_{50} values are available for a large number of compounds and can be estimated for a large number of compounds using software, such as T.E.S.T., this approach can provide estimates for a large number of compounds. However, further research is needed to determine whether these values yield more suitable estimates of lifetime risk than estimating an OED value from ToxCast data.

2.9. Life cycle thinking

Shin and coworkers recently developed a methodology to assess chemical exposures using near-field and far-field models and production volumes (Shin et al. 2015). They utilized several different models to estimate near-field exposure from indoor emissions (Bennett and Furtaw 2004; Shin et al. 2012; Wenger et al. 2012; Zhang et al. 2014). Similarly they estimated far-field exposure from several different multimedia mass balance models such as CalTox (McKone 1993), USEtox (Rosenbaum et al. 2008), and RAIDAR (Arnot et al. 2006). The intake estimates were combined with *in vitro* bioactivity data to demonstrate risk-based screening and prioritization of 180 chemicals (Shin et al. 2015). Fantke et al. developed a method to couple near- and far-field exposure pathways using multimedia-based transfer fractions to support Life Cycle Assessment (LCA), alternatives assessment, and risk assessment of chemicals used in consumer products (Fantke et al. 2016).

Emissions to the environment can be obtained from many different publicly available databases. Shin et al. (2015) obtained emissions data from the 2006 US EPA Inventory Update Reporting (IUR) (US EPA 2008), the National-Scale Air Toxics Assessments (NATA) (US EPA 2011b), the Toxics Release Inventory (TRI) Program (US EPA 2016g), and the National Emissions Inventory (NEI) (US EPA 2016d). Finally, the US EPA is developing a methodology to rapidly generate life cycle inventories (LCIs) from a variety of public data sources including TRI and NEI (Cashman et al. 2016). The methodology attempts to allocate the emissions from different facilities which are directly related to the production of the chemical of interest. The potential use categories of chemicals can be obtained from the US EPA's Chemical and Product Categories (CPCat) database (Dionisio et al. 2015; US EPA 2014b) within ACToR (US EPA 2016a). A more detailed review on publicly available exposure data is provided by Egeghy et al. (Egeghy et al. 2012).

For flame retardants, the highest exposure potential during the manufacture stage is during the handling of the raw flame retardant (European Chemicals Bureau 2002). For decaBDE, exposure is expected to occur dermally or through inhalation. Thus, pertinent toxicity endpoints during the manufacture stage include acute toxicity (dermal/inhalation), carcinogenicity, respiratory sensitization, neurotoxicity, skin sensitization, and skin and eye corrosion/irritation.

DecaBDE and other halogenated flame retardants have been detected in house dust (Stapleton et al. 2005). This illustrates that flame retardants which are physically incorporated into the polymer used (e.g. for the backing material) can be inhaled during the use stage. The primary route of consumer exposure to decaBDE is through the ingestion of dust or, for infants, ingestion of breast milk, followed by food and water ingestion and dermal absorption. Inhalation may also be a relevant route of exposure (US EPA 2010).

During the end of life stage, electronics containing flame retardants are either recycled or landfilled. Workers involved in the recycling and disposal of products containing flame retardants have greater exposure to the chemical when compared to the general population (Sjödén et al. 1999). The leachate from landfills have the potential to seep into groundwater or drain into surface water both of which facilitate transporting chemicals where humans and wildlife may be exposed (KemI 1995).

3. Results and discussion

3.1. Generation of transformation products

In this paper, evaluation of the metabolites and abiotic transformation products for decabromodiphenyl ether (decaBDE) and three phosphate based flame retardants: triphenyl phosphate (TPP), resorcinol bis-(diphenyl phosphate) (RDP), and bisphenol A bis(diphenyl phosphate) (BPADP) was conducted. DecaBDE is not predicted to degrade according to the reaction libraries for human metabolism or hydrolysis within CTS (Wolfe et al. 2016). However, common degradation products of decaBDE due to photodegradation, anaerobic biotransformation and metabolism in fish and birds include octaBDE and pentaBDE (Clean Production Action 2007). The metabolites for phosphate based non-halogenated alternatives, RDP and TPP, were generated using CTS. The transformation pathways for RDP are given in Figure 4. The products for RDP include benzenediol (1,2- and 1,3- substituted), phenol, and diphenyl phenol. Chemicals, such as phenol and benzenediol, are of concern because they are associated with endocrine activity. Unfortunately, experimental data on whether RDP releases these compounds are not available (US EPA 2014a). Similarly, the predicted products from human metabolism and abiotic hydrolysis for TPP include phenol and diphenyl phosphate. Transformation products for BPADP include bisphenol A, phenol, and diphenyl phosphate (Clean Production Action 2007). These additional chemicals will be considered when comparing alternatives.

3.2. Evaluation of physicochemical properties

The melting points and boiling points for all of the flame retardant alternatives were greater than 20 °C (see Table 2) indicating they will all be a solid at room temperature. Not surprisingly, the flame retardant alternatives all had very high flash points, indicating they are non-flammable. The majority of the compounds had very low vapor pressures indicating a low risk from inhalation of vapors (although triphenyl phosphate was borderline). Because the vapor pressure values were typically less than 1×10^{-8} , the risk would be due to inhalation of small particles, which would occur during the manufacturing stage by workers unless proper controls were enacted.

The majority of the flame retardants are insoluble in water (solubility < 1 mg/L) (US EPA 2014a). However, TPP is slightly soluble in water ($1 \text{ mg/L} < \text{solubility} < 100 \text{ mg/L}$) and RDP is almost as soluble as TPP. Most of the chemicals were predicted to have $\log K_{OW}$ greater than 8, indicating they are not readily bioavailable. TPP had a much lower $\log K_{OW}$, which indicates it may be bioavailable and thus has potential for aquatic toxicity. The predicted $\log BCF$ values indicated that the alternatives all had low to moderate bioaccumulation potential.

To estimate the persistence score, the partitioning for each alternative was estimated using a level III fugacity model included in EPISUITE (Mackay 1991; Mackay et al. 1996a; Mackay et al. 1996b; US EPA 2012). As shown in Table 3, the flame retardants partition predominantly to soil and sediment. Due to its relatively high water solubility, TPP partitions into the water compartment in a greater fraction than the other alternatives. Most of the flame retardant alternatives are predicted to have very high persistence with the exception of

TPP, which is predicted to have high persistence. The degradation products of decaBDE were also predicted to have very high persistence, whereas those for the phosphate-based flame retardants had high persistence (e.g. diphenyl phosphate) or moderate persistence (e.g. phenol).

3.3. Evaluation of human health hazards and ecotoxicity using T.E.S.T

The human health hazards and ecotoxicity values generated using T.E.S.T. for the decaBDE alternatives are given in Table 4. The flame retardant alternatives were found to have a low mammalian acute toxicity score ($LD_{50} > 2000$ mg/kg). A couple of the metabolites of phosphate-based flame retardants (phenol and resorcinol) had moderate toxicity (300 mg/kg $< LD_{50} < 2000$ mg/kg).

Developmental toxicity values could not be estimated for most of the flame retardants using the T.E.S.T. models (aside from TPP, which is predicted to be positive). This can be explained by the fact there are insufficient chemicals in the training set, which are similar to these relatively large compounds. Several of the degradation products of the phosphate-based flame retardants were predicted to have developmental toxicity values (diphenyl phosphate, bisphenol A, and phenol). None of the flame retardant alternatives are predicted to be mutagenic. However, diphenyl phosphate (a transformation product of the phosphate-based flame retardants) is predicted to be mutagenic. All of the flame retardant alternatives are predicted to have very high aquatic toxicity ($LC_{50} < 1$ mg/L). However, for decaBDE and BPADP, the predicted toxicity value exceeded the water solubility. For these compounds, the effective hazard score is low. (US EPA 2014a) TPP and RDP have much higher solubility in water and thus pose an aquatic toxicity hazard.

The hierarchical clustering model predictions for endocrine activity are given in Table 5. The predictions were made using models which were fit to training sets with 25% active compounds, because this was found to yield the best results for several endocrine activity endpoints (Martin 2016). A chemical is predicted to be active if the average predicted score from the hierarchical clustering models is greater than or equal to 0.5. For *in vitro* activity, the majority of the flame retardant alternatives were predicted to be inactive in terms of binding and agonism and active in terms of antagonism. If chemicals are endocrine active, there should be a positive result for both binding and either agonism or antagonism. DecaBDE and its degradates could not be predicted utilizing the *in vivo* endocrine activity models. This can be explained by the fact the *in vivo* models utilized a considerably smaller training set (~200 chemicals) and there were insufficient chemicals which were similar to these polybrominated compounds. The *in vivo* endocrine activity for TTP and RDP yielded conflicting results for the two *in vivo* models (with and without predicted *in vitro* scores as additional model descriptors). In addition, the predicted *in vitro* binding scores were less than 0.5, which would indicate these compounds inactive in terms of estrogen receptor activity. The conflicting prediction results indicate that experimental data is needed to make a definitive assignment for these compounds. Similarly BPADP has a positive prediction for one of the *in vivo* models (but the other is outside the applicability domain) and the predicted *in vitro* binding score is negative. One of the metabolites for BPADP, bisphenol A was predicted to be positive in all of the models indicating it poses a risk for endocrine

disruption. Because bisphenol A is a known endocrine disruptor and was not present in the training set for the *in vivo* models, this represents a successful external validation of the models.

3.4. Comparison of hazard profiles

The hazard profiles generated from T.E.S.T., a DfE (US EPA 2014a) study, a GreenScreen (Clean Production Action 2007) study, and the ChemHAT (Chemhat.org 2016) database for the flame retardant alternatives and their transformation products are given in Tables 6 and 7 respectively. The transformation products were not evaluated in the DfE study. Diphenyl phosphate was not present in ChemHAT and scores were not assigned in the GreenScreen study due to insufficient data. RDP is present in ChemHAT, but the only available hazard information is that this chemical is on a restricted list. In the GreenScreen study, data for BPADP and RDP were based on analog data or expert judgement. This illustrates the need to develop automated methodologies to find suitable analogs to fully populate hazard profiles.

The scores from ChemHAT were translated as follows: red = VH (very high effect/evidence), orange = H (high effect/evidence), yellow = M (moderate effect/evidence), and gray = ? (equivocal effect/evidence). The hazard categories (column headings) are not an exact match with scoring systems like DfE or GreenScreen but are close enough to allow for comparison. All of the alternatives and their metabolites are on restricted lists (not shown) according to ChemHAT.

The flame retardant alternatives have a low acute mammalian toxicity score, while the transformation products of TPP and RDP generally have a moderate acute mammalian toxicity. The transformation products of decaBDE had a low score. The phosphate-based flame retardants had the same score for carcinogenicity (either moderate from the DfE study or low from GreenScreen study). Both the DfE study and the GreenScreen study report a moderate score for carcinogenicity for decaBDE. However, decaBDE was reported to have a strong evidence of cancer risk according to ChemHAT.org (US EPA 2016c). This may indicate decaBDE may pose a greater cancer risk than the phosphate-based flame retardants.

For mutagenicity, all of the chemicals were predicted to have a negative score by T.E.S.T. (with the exception of diphenyl phosphate) (see Table 4). The other studies report low scores for mutagenicity for the flame retardant alternatives (although ChemHAT reports a high score for mutagenicity for decaBDE). The GreenScreen study and ChemHAT report a positive result for mutagenicity for phenol while the experimental and predicted value for the Ames mutagenicity endpoint in T.E.S.T. were negative.

DecaBDE and its transformation products had medium or high endocrine disruption scores. TPP, RDP, and BPADP had little information for endocrine disruption. Bisphenol A (a metabolite of BPADP) was the only chemical which was definitively predicted to be an endocrine disrupter using the hierarchical clustering models (Martin 2016).

The flame retardants had a low score for reproductive effects (see Table 6), but transformation products such as pentaBDE and octaBDE had medium to very high reproductive scores. DecaBDE and its products had the highest developmental toxicity

scores. In terms of neurological toxicity, again decaBDE and its metabolites had the highest scores. In terms of repeated dose toxicity, triphenyl phosphate had the highest scores.

As mentioned previously, most of the alternatives did not have a predicted developmental toxicity value (these chemicals were outside the applicability domain of the models) using T.E.S.T. However, TPP and its transformation products (phenol and diphenyl phosphate) were predicted to be active in terms of developmental toxicity and thus the developmental toxicity scores were high. Some metabolites of BPADP were also predicted to be active in terms of developmental toxicity. In terms of neurological toxicity, TPP and BPADP had a low score while the scores for decaBDE and RDP varied from low to very high. Most of the alternatives had a moderate score for repeated dose toxicity although TPP had a high score from the DfE study.

The flame retardants did not pose a risk for skin sensitization (aside from the metabolites bisphenol A and resorcinol). The alternatives had low to moderate score for eye irritation. Similarly, dermal irritation is a low concern. Phenol has a high score for eye and dermal irritation but it is doubtful humans will be exposed to high enough concentrations of phenol through these routes for this to be an issue (since the flame retardant has to be metabolized by the body or undergo hydrolysis in a body of water first).

In terms of acute aquatic toxicity, RDP and TPP yielded the highest scores due to their relatively high solubilities in water. DecaBDE and BPADP had low scores due to the fact that the toxicity values exceeded their water solubilities. A similar result was observed for chronic aquatic toxicity.

With the exception of TPP, all of the flame retardant alternatives were predicted to have a very high persistence score utilizing the multimedia models in EPISUITE. DecaBDE had very high persistence scores for all studies, while the scores for the other flame retardant alternatives varied from low to high using the DfE and GreenScreen scores. The transformation products for RDP and TPP were much less persistent than those for decaBDE. The columns for persistence and bioaccumulation for ChemHAT rows are merged because ChemHAT reports whether some chemicals are PBT chemicals from international lists and does not always have a separate score for both persistence and bioaccumulation.

All of the chemicals had low or medium bioaccumulation using the models from T.E.S.T. The bioaccumulation scores for the flame retardants varied from low to high depending on the data source. The transformation products of the phosphate-based flame retardants had low scores for bioaccumulation compared to scores of moderate to very high for the products of decaBDE.

The main concern for decaBDE is that it has very high persistence. It also has concerns for carcinogenicity, developmental toxicity, endocrine disruption, and neurological toxicity. Its transformation products (pentaBDE and octaBDE) also pose similar concerns. The main concern for TPP is aquatic toxicity, although the lower persistence score would indicate this might not be a large concern. Another concern for TPP is repeated dose toxicity. BPADP poses low concern for most hazard categories however its metabolite bisphenol A has concerns for several effects, most notably endocrine disruption. The main concern for RDP

is the very high aquatic toxicity and moderate persistence. The human health hazards for RDP are low to moderate depending on the source. Diphenyl phosphate is a potential product for all three phosphate-based flame retardants. According to T.E.S.T. models, diphenyl phosphate poses concerns for mutagenicity and developmental toxicity. Taking all of these factors into consideration, TPP and RDP appear to be the best alternatives. An exposure/risk assessment over the entire life cycle will be needed to more quantitatively identify and select the best alternative.

3.5. Evaluation of exposure and risk over the product life cycle

Arnot and coworkers (Arnot and Mackay 2008; Arnot et al. 2006) calculated RAF values for many different compounds using far-field multimedia models. DecaBDE and bis(hexachlorocyclopentadieno) cyclooctane were found to have similar RAF values (10^{-4} $\text{RAF} < 10^{-2}$) for both level II and level III fugacity models. This makes sense because these compounds are both high molecular weight, polyhalogenated compounds. Unfortunately, Arnot and coworkers did not evaluate phosphate-based flame retardants for comparison.

Shin and coworkers (Shin et al. 2015) utilized both near-field and far-field models to better characterize exposure from chemical products. The BQ (see equation 3) of triphenyl phosphate was found to be greater than 100 for four use scenarios in part because of its large production volume and its low minimum OED. This might indicate that TPP is not the best alternative despite its lower environmental persistence. Initial development of this alternatives assessment dashboard will not include consideration of exposure and risk until methods can be developed (such as in the ExpoCast project) to fully automate the process of obtaining emission data and estimating risk for a wide variety of chemical products.

Jonkers et al (2016) conducted a life cycle assessment of flame retardants incorporated into a commercial product, i.e. a laptop computer. They compared results for brominated flame retardants (BFRs) and halogen-free flame retardants (HFFRs). The largest differences in impact were found to occur in the waste phase due to an increased dioxin emission formed from BFRs during improper waste treatment. Minor human toxicity and ecotoxicity impacts of FRs are present due to volatilization in the use phase. Over the full life cycle, the BFR scenario has a slightly higher environmental impact than the HFFR scenario, mainly through the contribution of human toxicity in the waste phase. However, it must be noted that Jonkers et al. (2016) used disability adjusted life years (DALY) as their indicator of human toxicity. Because the DALY values for the two phosphate-based flame retardants in the study (RDP and BPADP) were not available, it was not possible to get an indication of the relative impact of human toxicity over the entire life cycle for these compounds relative to decaBDE. This illustrates the benefits of using QSAR models or *in vitro*-based methods for filling data gaps. It is interesting to note that during the use phase, the scores for human toxicity and ecotoxicity are two orders of magnitude higher for electricity use of the laptop than for the volatilization of the FRs used in the backing. However, emissions during the use phase are still likely to be the most important exposure route for humans. This study shows that one needs to consider likely exposure scenarios throughout the entire life cycle in order to realistically compare alternatives.

4. Conclusions

A two stage AA methodology for comparing chemical alternatives based on the National Research Council's Chemical Alternatives framework document was successfully implemented. In the first stage, alternatives are compared using a variety of human health effects, ecotoxicity, and physical properties. Additional work is needed to generate complete hazard profiles for a large number of chemicals. For example, experimental data needs to be compiled from a variety of freely available online sources, QSAR models need to be developed for additional toxicity endpoints, and a user-friendly system for obtaining experimental analog data for endpoints which are not amenable to QSAR modeling needs to be developed. In the second stage, alternatives are evaluated utilizing an exposure/risk assessment over the entire life cycle. The second stage allows one to more accurately compare exposure potential for each alternative and consider additional factors that may not be obvious from separate binned persistence, bioaccumulation, and toxicity scores.

References

- Arnot J, Brown T, Wania F, Breivik K, McLachlan M. Prioritizing Chemicals and Data Requirements for Screening-Level Exposure and Risk Assessment. *Environ Health Persp.* 2012; 120:1565–1570.
- Arnot JA, Mackay D. Policies for Chemical Hazard and Risk Priority Setting: Can Persistence, Bioaccumulation, Toxicity, and Quantity Information Be Combined? *Environ Sci Technol.* 2008; 42:4648–4654. DOI: 10.1021/es800106g [PubMed: 18677986]
- Arnot JA, Mackay D, Parkerton TF, Zaleski RT, Warren CS. Multimedia modeling of human exposure to chemical substances: The roles of food web biomagnification and biotransformation. *Environ Toxicol Chem.* 2010; 29:45–55. [PubMed: 20821418]
- Arnot JA, Mackay D, Webster E, Southwood JM. Screening Level Risk Assessment Model for Chemical Fate and Effects in the Environment. *Environ Sci Technol.* 2006; 40:2316–2323. DOI: 10.1021/es0514085 [PubMed: 16646468]
- Bennett DH, Furtaw EJ. Fugacity-Based Indoor Residential Pesticide Fate Model. *Environ Sci Technol.* 2004; 38:2142–2152. DOI: 10.1021/es034287m [PubMed: 15112818]
- Cashman S, et al. Mining Public Data from the United States Environmental Protection Agency to Support Rapid Life Cycle Inventory Modeling of Chemical Manufacturing Accepted for publication to *Environmental Science and Technology*. 2016
- ChemAxon. [Accessed 7/29/16] Physico-chemical property predictors. Calculations and predictions of essential physico-chemical characteristics. 2016. <https://www.chemaxon.com/products/calculator-plugins/property-predictors/>
- Chemhat.org. Chemical Hazards and Alternatives Toolbox. 2016.
- Chen D, Hale RC. A global review of polybrominated diphenyl ether flame contamination in birds. *Environ Int.* 2010; 36:800–811. [PubMed: 20557935]
- Clean Production Action. [Accessed 7/23/16] The Green Screen for safer chemicals: evaluating flame retardants for TV enclosures. 2007. http://www.greenscreenchemicals.org/static/ee_images/uploads/resources/EvaluatingFlameRetardants_GreenScreenSaferChemicals_2007.pdf
- Cohen Hubal EA, et al. Advancing Exposure Characterization for Chemical Evaluation and Risk Assessment. *J Toxicol Environ Health B Crit Rev.* 2010; 13:299–313. DOI: 10.1080/10937404.2010.483947 [PubMed: 20574904]
- D'Silva K, Fernandes A, Rose M. Brominated organic micropollutants- igniting the flame retardant issue. *Crit Rev Environ Sci Technol.* 2004; 34:141–207.
- Danish Ministry of the Environment's Environmental Protection Agency. [Accessed 7/22/16] <http://eng.mst.dk/topics/chemicals/assessment-of-chemicals/the-advisory-list-for-selfclassification/>
- Dionisio KL, et al. Exploring consumer exposure pathways and patterns of use for chemicals in the environment. *Toxicol Rep.* 2015; 2:228–237. [PubMed: 28962356]

- Egeghy PP, Judson R, Gangwal S, Mosher S, Smith D, Vail J, Cohen Hubal EA. The exposure data landscape for manufactured chemicals. *Sci Total Environ*. 2012; 414:159–166. doi:<http://dx.doi.org/10.1016/j.scitotenv.2011.10.046>. [PubMed: 22104386]
- Environment Canada. [Accessed 7/22/16] Ecological Screening Assessment Report on Polybrominated Diphenyl Ethers (PBDEs). 2006. <https://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=0DDA2F24-1>
- European Chemicals Agency. [Accessed 7/22/16] C&L Inventory. 2016. <http://echa.europa.eu/information-on-chemicals>
- European Commission. [Accessed 7/29/16] The Directive on Dangerous Substances. 2008. http://ec.europa.eu/environment/archives/dansub/home_en.htm
- European Union. [Accessed 7/29/16] Classification and Labelling (CLP/GHS). 2008. https://ec.europa.eu/growth/sectors/chemicals/classification-labelling_en
- Fantke, P., Ernststoff, AS., Huang, L., Csiszar, SA., Jolliet, O. Coupled near-field and far-field exposure assessment framework for chemicals in consumer products. *Environ Int*. 2016. In press doi:<http://dx.doi.org/10.1016/j.envint.2016.06.010>
- Fukata H, Omori M, Osada H, Todaka E, Mori C. Necessity to measure PCBs and organochlorine pesticide concentrations in human umbilical cords for fetal exposure assessment. *Environ Health Perspect*. 2005; 113:297–303. [PubMed: 15743718]
- Illinois Environmental Protection Agency. [Accessed 7/22/16] A Report to the General Assembly and the Governor In Response to Public Act 94–100 DecabDE Study: A Review of Available Scientific Research. 2006. <http://www.epa.state.il.us/reports/decabde-study/available-research-review.pdf>
- International Agency for Research on Cancer (IARC). Agents Classified by the IARC Monographs. 2016; 1–116 [Accessed 7/22/16] <http://monographs.iarc.fr/ENG/Classification/>.
- Isaacs KK, et al. SHEDS-HT: An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources. *Environ Sci Technol*. 2014; 48:12750–12759. DOI: 10.1021/es502513w [PubMed: 25222184]
- Jonkers N, Krop H, van Ewijk H, Leonards PEG. Life cycle assessment of flame retardants in an electronics application. *Int J Life Cycle Assess*. 2016; 21:146–161. DOI: 10.1007/s11367-015-0999-z
- KemI. PM nr 10/95. The Swedish Chemicals Inspectorate; Solna, Sweden: 1995. The Flame Retardants Project – A collection of reports on some flame- retardants and an updated ecotoxicological summary for tetrabromobisphenol A.
- Mackay, D. The Fugacity Approach. Lewis Publishers, CRC Press; 1991. Multimedia Environmental Models; p. 67-183.
- Mackay D, Di Guardo A, Paterson S, Cowan CE. Evaluating the environmental fate of a variety of types of chemicals using the EQC model. *Environ Toxicol Chem*. 1996a; 15:1627–1637. DOI: 10.1002/etc.5620150929
- Mackay D, Di Guardo A, Paterson S, Kicsi G, Cowan CE. Assessing the fate of new and existing chemicals: A five-stage process. *Environ Toxicol Chem*. 1996b; 15:1618–1626. DOI: 10.1002/etc.5620150928
- Martin MT, Knudsen TB, Reif DM, Houck KA, Judson RS, Kavlock RJ, Dix DJ. Predictive Model of Rat Reproductive Toxicity from ToxCast High Throughput Screening. *Biol Reprod*. 2011; 85:327–339. DOI: 10.1095/biolreprod.111.090977 [PubMed: 21565999]
- Martin TM. Prediction of in vitro and in vivo oestrogen receptor activity using hierarchical clustering SAR QSAR. *Environ Res*. 2016; 27:17–30. DOI: 10.1080/1062936X.2015.1125945
- Martin TM, Harten P, Venkatapathy R, Das S, Young DM. A Hierarchical Clustering Methodology for the Estimation of Toxicity. *Toxicol Mech Methods*. 2008; 18:251–266. DOI: 10.1080/15376510701857353 [PubMed: 20020919]
- McKone, TE. [Accessed 7/19/16] CalTOX, A Multimedia Total-Exposure Model for Hazardous Waste Sites. 1993. <http://www.osti.gov/scitech/servlets/purl/139702>
- McLachlan MS, Czub G, MacLeod M, Arnot JA. Bioaccumulation of Organic Contaminants in Humans: A Multimedia Perspective and the Importance of Biotransformation. *Environ Sci Technol*. 2011; 45:197–202. DOI: 10.1021/es101000w [PubMed: 20701275]

- National Institute of Technology and Evaluation (NITE). [Accessed 7/22/16] GHS Classification Results. 2016. http://www.safe.nite.go.jp/english/ghs/all_fy_e.html
- National Research Council. A Framework to guide selection of chemical alternatives. National Research Council; 2014. <http://www.nap.edu/catalog/18872/a-framework-to-guide-selection-of-chemical-alternatives> [Accessed 10/16/15]
- Niemelä, JR., Wedebye, EB., Nikolov, NG., Ringsted, GEJoT. The Advisory list for self-classification of dangerous substances CLP-version, Ver. 3. Division of Toxicology and Risk Assessment, Technical University of Denmark; Kongens Lyngby, Denmark: 2010.
- OECD. [Accessed 8/23/16] OECD Guideline for Test No. 301: Ready Biodegradability. 1992. http://www.oecd-ilibrary.org/environment/test-no-301-ready-biodegradability_9789264070349-en
- Office of Pollution Prevention & Toxics USEPA. Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation Version 2.0. 2011.
- Pharos. [Accessed 7/29/16] Pharos Chemical and Material Library (CML). 2016. <https://www.pharosproject.net/material/chemical>
- Rosenbaum RK, et al. USEtox—the UNEP-SETAC toxicity model: recommended characterisation factors for human toxicity and freshwater ecotoxicity in life cycle impact assessment. *Int J Life Cycle Assess.* 2008; 13:532–546. DOI: 10.1007/s11367-008-0038-4
- Rosenbaum RK, et al. USEtox human exposure and toxicity factors for comparative assessment of toxic emissions in life cycle analysis: sensitivity to key chemical properties. *Int J Life Cycle Assess.* 2011; 16:710–727. DOI: 10.1007/s11367-011-0316-4
- Shin H-M, et al. Risk-Based High-Throughput Chemical Screening and Prioritization using Exposure Models and in Vitro Bioactivity Assays. *Environ Sci Technol.* 2015; 49:6760–6771. DOI: 10.1021/acs.est.5b00498 [PubMed: 25932772]
- Shin H-M, McKone TE, Bennett DH. Intake Fraction for the Indoor Environment: A Tool for Prioritizing Indoor Chemical Sources. *Environ Sci Technol.* 2012; 46:10063–10072. DOI: 10.1021/es3018286 [PubMed: 22920860]
- Sjödin A, Hagmar L, Klasson-Wehler E, Kronholm-Diab K, Jakobsson E, Bergman A. Flame retardant exposure: polybrominated diphenyl ethers in blood from Swedish workers. *Environ Health Persp.* 1999; 107:643–648.
- Stapleton HM, Dodder NG, Offenberger JH, Schantz MM, Wise SA. Polybrominated Diphenyl Ethers in House Dust and Clothes Dryer Lint. *Environ Sci Technol.* 2005; 39:925–931. DOI: 10.1021/es0486824 [PubMed: 15773463]
- The Lowell Center for Sustainable Production. [Accessed 7/11/16 2016] Decabromodiphenylether: An Investigation of Non-Halogen Substitutes in Electronic Enclosure and Textile Applications. 2005. <http://www.sustainableproduction.org/downloads/DecaBDESubstitutesFinal4-15-05.pdf>
- Thomas RS, et al. A Comprehensive Statistical Analysis of Predicting In Vivo Hazard Using High-Throughput In Vitro Screening. *Toxicol Sci.* 2012; 128:398–417. DOI: 10.1093/toxsci/kfs159 [PubMed: 22543276]
- U.S. National Library of Medicine. [Accessed 7/22/16] Hazardous Substances Databank. 2016. <https://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>
- UNECE. [Accessed 7/25/16] Globally Harmonized System of Classification and Labelling of Chemicals (GHS). 2007. http://www.unece.org/trans/danger/publi/ghs/ghs_rev02/02files_e.html
- US EPA. [Accessed 7/19/16] Using the 2006 Inventory Update Reporting (IUR) Public Data: Background Document. 2008. https://www.epa.gov/sites/production/files/documents/iurdbbbackground_0.pdf
- US EPA. [Accessed 7/26/16] An exposure assessment of polybrominated diphenyl ethers. 2010. <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=210404&CFID=66107585&CFTOKEN=76035728>
- US EPA. [Accessed 7/28/16] Design for the environment program alternatives assessment criteria for hazard evaluation. Version 2.0. 2011a. <https://www.epa.gov/saferchoice/alternatives-assessment-criteria-hazard-evaluation>
- US EPA. [Accessed 7/19/16] National-Scale Air Toxics Assessment. 2011b. <https://www.epa.gov/national-air-toxics-assessment>

- US EPA. EPI Suite Version 4.11. Syracuse Research Corporation; 2012. <https://www.epa.gov/tsca-screening-tools/epi-suite-estimation-program-interface> [Accessed 7/24/16]
- US EPA. [Accessed 7/11/16 2016] An alternatives assessment for the flame retardant decabromodiphenyl ether. 2014a. https://www.epa.gov/sites/production/files/2014-05/documents/decabde_final.pdf
- US EPA. [Accessed 7/19/16] Chemical and Product Categories (CPCat) database. 2014b. <http://actor.epa.gov/cpcat/faces/home.xhtml>
- US EPA. [Accessed 7/22/16] ACToR (Aggregated Computational Toxicology Resource). 2016a. <https://actor.epa.gov/actor/>
- US EPA. [Accessed 7/22/16] ECOTOX Knowledgebase. 2016b. <https://cfpub.epa.gov/ecotox/>
- US EPA. [Accessed 7/22/16] Integrated Risk Information System (IRIS). 2016c. <https://www.epa.gov/iris>
- US EPA. National Emissions Inventory. 2016d. <https://www.epa.gov/air-emissions-inventories/national-emissions-inventory>
- US EPA. Reviewing New Chemicals under the Toxic Substances Control Act (TSCA). 2016e. <https://www.epa.gov/reviewing-new-chemicals-under-toxic-substances-control-act-tsca>
- US EPA. [Accessed 7/24/16] T.E.S.T. Version 4.2. 2016f. <http://www2.epa.gov/chemical-research/toxicity-estimation-software-tool-test>
- US EPA. Toxics Release Inventory (TRI) Program. 2016g. <https://www.epa.gov/toxics-release-inventory-tri-program>
- Vermeire T, et al. European union system for the evaluation of substances: the second version. *Chemosphere*. 2005; 59:473–485. doi:<http://dx.doi.org/10.1016/j.chemosphere.2005.01.062>. [PubMed: 15788170]
- Vermeire TG, et al. European Union System for the Evaluation of Substances (EUSES). Principles and structure *Chemosphere*. 1997; 34:1823–1836. doi:[http://dx.doi.org/10.1016/S0045-6535\(97\)00017-9](http://dx.doi.org/10.1016/S0045-6535(97)00017-9). [PubMed: 9114488]
- Wambaugh JF, et al. High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project. *Environ Sci Technol*. 2013; 47:8479–8488. DOI: 10.1021/es400482g [PubMed: 23758710]
- Wambaugh JF, Wang A, Dionisio KL, Frame A, Egeghy P, Judson R, Setzer RW. High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals. *Environ Sci Technol*. 2014; 48:12760–12767. DOI: 10.1021/es503583j [PubMed: 25343693]
- Wehage K, Chenhansa P, Schoenung JM. An open framework for automated chemical hazard assessment based on GreenScreen for Safer Chemicals: A proof of concept. *Integr Environ Assess Manag*. 2016; n/a-n/a. doi: 10.1002/ieam.1763
- Wenger Y, Li D, Jolliet O. Indoor intake fraction considering surface sorption of air organic compounds for life cycle assessment. *Int J Life Cycle Assess*. 2012; 17:919–931. DOI: 10.1007/s11367-012-0420-0
- Weschler CJ, Nazaroff WW. SVOC partitioning between the gas phase and settled dust indoors. *Atmospheric Environment*. 2010; 44:3609–3620. doi:<http://dx.doi.org/10.1016/j.atmosenv.2010.06.029>.
- Wetmore BA, et al. Incorporating High-Throughput Exposure Predictions With Dosimetry-Adjusted In Vitro Bioactivity to Inform Chemical Toxicity Testing. *Toxicol Sci*. 2015; 148:121–136. DOI: 10.1093/toxsci/kfv171 [PubMed: 26251325]
- Wikipedia.org. Decabromodiphenyl ether. 2016. https://en.wikipedia.org/wiki/Decabromodiphenyl_ether#Voluntary_and_governmental_actions
- Wilson MP, Hammond SK, Nicas M, Hubbard AE. Worker Exposure to Volatile Organic Compounds in the Vehicle Repair Industry. *J Occup Environ Hyg*. 2007; 4:301–310. DOI: 10.1080/15459620701258021 [PubMed: 17454499]
- Wolfe, K., et al. Chemical Transformation System: Cloud Based Cheminformatic Services to Support Integrated Environmental Modeling. In: Sabine Sauvage, J-MS-PaAER., editor. International Environmental Modelling and Software Society (iEMSs); 8th Intl. Congress on Env. Modelling and Software; Toulouse, France. 2016.

Zhang X, Arnot JA, Wania F. Model for Screening-Level Assessment of Near-Field Human Exposure to Neutral Organic Chemicals Released Indoors. *Environ Sci Technol*. 2014; 48:12312–12319. DOI: 10.1021/es502718k [PubMed: 25264817]

EPA Author Manuscript

EPA Author Manuscript

EPA Author Manuscript

Fig. 1. Stage 1 of the alternatives assessment methodology: generation of hazard profiles. *GHS = global harmonization score

Fig. 2.
Stage 2 of the alternatives assessment methodology: evaluation of exposure/risk

Risk phrase ^a	R28		R25		R22		
LD50, mg/kg	≤5	5-25	25-50	50-200	200-300	300-2000	2000-5000
GHS ^b	Cat 1	Category 2		Category 3		Category 4	Category 5
EU CLP ^c	H300		H301		H302		H303
DfE Score ^d	Very high		High		Moderate		Low

Fig. 3.
 Converting between scoring systems. a (European Commission 2008), b (UNECE 2007), c (European Union 2008), d (US EPA 2011a)

a) Degradation products from human metabolism

b) Degradation products from abiotic hydrolysis

Fig. 4.
Degradation products for RDP from CTS (Wolfe et al. 2016)

Table 1

Relevance of physicochemical properties

Property range	Result
melting point < ambient temperature	Solid phase (unless dissolved in water)
melting point < ambient temperature < boiling point	Liquid phase
ambient temperature > boiling point	Vapor phase
vapor pressure < 1×10^{-6} mm Hg	Low potential for inhalation exposure (unless in solid microparticles)
vapor pressure > 1×10^{-4} mm Hg	Exist in the gas phase in the atmosphere
1×10^{-8} < vapor pressure < 1×10^{-4}	Exist as a gas/particulate mixture
vapor pressure < 1×10^{-8} mm Hg	Exist as a particulate
Water solubility < 0.01 mg/L	Lower concern for both the expression of adverse effects, and potential aquatic and general population exposure due to their low bioavailability.
estimated toxicity mg/L > water solubility	Adverse effect cannot be reached, low potential from harm from aquatic toxicity
$\log K_{OW} > 8$	Insoluble in water and not readily bioavailable
flash point > 37.8 C	Non-flammable
Half-life* > 180 days	Very high persistence
60 Half-life 180 days	High persistence
16 Half-life < 60 days	Moderate persistence
Half-life < 16 days	Low Persistence
$\log BCF > 3.7$	Very high bioaccumulation
$3 < \log BCF < 3.7$	High bioaccumulation
$2 < \log BCF < 3$	Moderate bioaccumulation
$\log BCF < 2$	Low bioaccumulation

* Half-life in the predominant compartment

Table 2

Physicochemical properties. All properties were estimated using T.E.S.T. (US EPA 2016f) with exception of log K_{OW} which was estimated with EPI Suite (US EPA 2012).

CAS	Name	MP*, °C	BP, °C	FP, °C	VP, mmHg
1163-19-5	Decabromodiphenyl Ether (decaBDE)	295 ^e	530 ^e	241 ^e	3.01E-12
115-86-6	Triphenyl Phosphate (TPP)	51 ^e	381	201 ^e	6.28E-06 ^e
57583-54-7	Resorcinol bis-(diphenyl phosphate) (RDP)	87	446	307	4.76E-08
5945-33-5	Bisphenol A bis(diphenyl phosphate) (BPADP)	114	435	378 ^e	4.21E-10
838-85-7	Diphenyl phosphate	68 ^e	357	168	3.17E-06
80-05-7	Bisphenol A	153 ^e	355	227 ^e	1.13E-06
108-95-2	Phenol	41 ^e	182 ^e	73 ^e	3.50E-01 ^e
108-46-3	Resorcinol	111 ^e	280 ^e	132 ^e	4.89E-04 ^e
32534-81-9	Pentabromodiphenyl Ether (pentaBDE)	222	438	206	1.52E-08
32536-52-0	Octabromodiphenyl Ether (octaBDE)	270	509	236	6.16E-11

CAS	Name	WS, mg/L	log K _{OW}	log BCF
1163-19-5	Decabromodiphenyl Ether (decaBDE)	1.00E-04 ^e	12.11	1.20 ^e
115-86-6	Triphenyl Phosphate (TPP)	1.90E+00 ^e	4.70	2.48 ^e
57583-54-7	Resorcinol bis-(diphenyl phosphate) (RDP)	2.90E-01	7.41	1.82
5945-33-5	Bisphenol A bis(diphenyl phosphate) (BPADP)	9.19E-02	10.02	1.28
838-85-7	Diphenyl phosphate	2.12E+02	2.88	1.66
80-05-7	Bisphenol A	1.20E+02 ^e	3.32 ^e	1.39 ^e
108-95-2	Phenol	8.27E+04 ^e	1.46 ^e	0.55 ^e
108-46-3	Resorcinol	7.18E+05 ^e	0.80 ^e	0.82
32534-81-9	Pentabromodiphenyl Ether (pentaBDE)	3.65E-03	8.50	2.41
32536-52-0	Octabromodiphenyl Ether (octaBDE)	1.70E-04	10.33	2.46

* MP = melting point, BP = boiling point, FP = flash point, VP = vapor pressure, WS = water solubility, log K_{OW} = log of the octanol water partition coefficient.
^e experimental value

Table 3
Partitioning and persistence results for level III fugacity model from EPISUITE (US EPA 2012)

Name	Mass amount, %				HL*, days
	Air	Water	Soil	Sediment	
DecaBDE	0.114	4.26	95.6	2.36E-03	360
TPP	0.513	13.8	77.1	8.6	75
RDP	1.05E-05	1.49	39.7	58.9	338
BPA DP	1.09E-06	1.1	41.8	57.1	542
Diphenyl phosphate	2.87E-03	13.7	86.1	0.208	75
Bisphenol A	6.77E-05	8.31	74.1	17.6	75
Phenol	7.88E-01	25.4	73.6	0.231	30
Resorcinol	1.74E-03	17.6	82.2	0.193	30
PentaBDE	1.84E-01	4.67	94.4	0.741	360
OctaBDE	1.15E-01	4.28	95.6	0.0507	360

* Half-life in the predominant compartment

Table 4

Human health hazards and ecotoxicity values from T.E.S.T. (US EPA 2016f)

CAS	Chemical	Oral rat LD ₅₀ , mg/kg	Developmental Toxicity	Muta-genicity	Fathead minnow LC ₅₀ mg/L
1163-19-5	Decabromodiphenyl Ether (decaBDE)	>5000 ^e	N/A	- ^e	6.44E-04
1115-86-6	Triphenyl Phosphate (TPP)	3496 ^e	+	- ^e	9.30E-01 ^e
57583-54-7	Resorcinol bis-(diphenyl phosphate) (RDPP)	2216	N/A	-	3.15E-02
5945-33-5	Bisphenol A bis(diphenyl phosphate) (BPADP)	2261	N/A	-	7.30E-01
838-85-7	Diphenyl phosphate	1829	+	+	5.60E-01
80-05-7	Bisphenol A	3247 ^e	+	- ^e	4.65E+00 ^e
108-95-2	Phenol	317 ^e	+	- ^e	3.01E+01 ^e
108-46-3	Resorcinol	301 ^e	- ^e	- ^e	5.49E+01 ^e
32534-81-9	PentaBDE	5000 ^e	N/A	-	8.79E-02
32536-52-0	OctaBDE	>5000	N/A	-	9.06E-03

^e experimental value

Table 5

Prediction of endocrine activity using hierarchical clustering (HC) models

Name	<i>In vitro</i> HC model			<i>In vivo</i> HC model	
	binding	agonism	antagonism	no <i>in vitro</i> *	with <i>in vitro</i>
DecaBDE	0.08	0.37	1.02	N/A	N/A
TPP	0.23	0.35	0.36	0.84	0.09
RDP	0.01	0.53	0.81	0.40	0.98
BPADP	0.21	0.51	0.88	0.86	N/A
Diphenyl phosphate	0.18	0.33	-0.05	0.38	0.40
Bisphenol A	0.73	0.92	0.53	0.93	1.30
Phenol	N/A	0.21	0.08	0.23	N/A
Resorcinol	0.37	0.21	0.22	0.33	-0.15
PentaBDE	-0.02	0.44	0.75	N/A	N/A
OctaBDE	0.11	0.45	1.02	N/A	N/A

* *In vivo* model utilizes predicted *in vitro* scores as additional descriptors

Table 6

Hazard profiles for the flame retardant alternatives (VL = Very Low, L = Low, M = Moderate, H = High, VH = Very High, nd = not determined, and ? = equivocal effect/evidence). Blanks indicate the chemical was not evaluated by the study or that hazard was not available in ChemHat.org.

Tool/Study	CAS ----- Name	Human Health Effects										Ecotox.			Fate	
		Acute Toxicity	Carcinogenicity	Genotoxicity/Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
TE.S.T.	1163-19-5 DecaBDE	L	nd	L	nd	nd	nd	nd	nd	nd	nd	nd	L	nd	VH	L
DfE		L	M	L	nd	L	H	L	M	L	L	L	L	L	VH	H
GreenScreen		L	M	L	M	L	M	M	L	L	L	L	L	L	VH	M
ChemHAT		M	VH	H	H	H	VH				M	M			VH	
TE.S.T.	115-86-6 TPP	L	nd	L	nd	nd	H	nd	nd	nd	nd	nd	VH	nd	H	M
DfE		L	M	L	nd	L	L	L	H	L	L	VL	VH	VH	L	M
GreenScreen		L	L	L	nd	L	L	L	M	L	M	L	H	H	L	M
ChemHAT		M			H			?			M		H	H		
TE.S.T.	57583-54-7 RDP	L	nd	L	nd	nd	nd	nd	nd	nd	nd	nd	VH	nd	VH	L
DfE		L	M§	L	nd	L	M	M	M	L	L	VL	VH	VH	M	H
GreenScreen§		L	L	L	nd	L	L	L	M	L	M	L	L	H	M	H
ChemHAT																
TE.S.T.	5945-33-5 BPADP	L	Nd	L	nd	nd	nd	nd	nd	nd	nd	nd	L	nd	VH	L
DfE		L	M	L	nd	L	L§	L§	L	L	L	L	L	L	H	H
GreenScreen§		L	L	L	nd	L	L	L	M	L	M	L	L	L	H	L
ChemHAT																

[§] based on analog data or expert judgement

Comparison of hazard profiles for the transformation products of flame retardant alternatives (VL = Very Low, L = Low, M = Moderate, H = High, VH = Very High, nd = not determined, and ? = equivocal effect/evidence). Blanks indicate the chemical was not evaluated by the study or that hazard was not available in ChemHat.org.

Table 7

Tool/Study	CAS ----- Name	Human Health Effects										Ecotox.			Fate	
		Acute Toxicity	Carcinogenicity	Genotoxicity/Mutagenicity	Endocrine Disruption	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
TE.S.T.	838-85-7 Diphenyl phosphate GreenScreen ChemHAT	M	nd	H	nd	nd	H	nd	nd	nd	nd	nd	VH	nd	H	L
TE.S.T.		L	nd	L	H	nd	H	nd	nd	nd	nd	nd	H	nd	H	L
GreenScreen		L	L	L	H	M	M	nd	M	M	H	L	M	M	L	L
ChemHAT	838-85-7 Bisphenol A GreenScreen ChemHAT	H		H	H	VH	H			H	H	M	H			
TE.S.T.		M	nd	L	nd	nd	H	nd	nd	nd	nd	nd	M	nd	M	L
GreenScreen		M	L	M	L	L	L	M	H	L	H	H	M	M	L	L
ChemHAT	108-95-2 Phenol GreenScreen ChemHAT	H	H	H	H	VH	M	?			H	H	H			
TE.S.T.		M	nd	L	nd	nd	L	nd	nd	nd	nd	nd	M	nd	M	L
GreenScreen		M	L	L	M	L	L	M	nd	M	M	M	M	M	L	L
ChemHAT	108-46-3 Resorcinol GreenScreen ChemHAT	H	?	H	H						M	M	H			
TE.S.T.		L	nd	L	nd	nd	nd	nd	nd	nd	nd	nd	L	nd	VH	M
GreenScreen		L	nd	L	H	M	M	M	H	L	M	M	H	H	VH	VH
ChemHAT	32534-81-9 PentaBDE GreenScreen ChemHAT	M	?		H		H	VH					H	H	VH	
TE.S.T.		L	nd	L	nd	nd	nd	nd	nd	nd	nd	nd	L	nd	VH	M
GreenScreen		L	nd	L	M	M	H	M								
ChemHAT	32536-52-0 OctaBDE GreenScreen ChemHAT	L	nd	L	M	M	H	M	H	L	L	L	L	L	VH	M
TE.S.T.		L	nd	L	nd	nd	nd	nd	nd	nd	nd	nd	L	nd	VH	M
GreenScreen		L	nd	L	M	M	H	M								
ChemHAT			?	H	H	VH	H	VH							VH	