UNIVERSITY OF CALIFORNIA
RIVERSIDE

A Screening-Level Hazard Assessment of Human and Environmental Health Endpoints of Halogenated and Organophosphate Flame Retardants

A Thesis submitted in partial satisfaction
of the requirements for the degree of

Master of Science

in

Environmental Toxicology

by

Seth Rojello Fernández

March 2019

Thesis Committee:
Dr. David Eastmond, Chairperson
Dr. Carl Cranor
Dr. David Volz

The Thesis of Seth Rojello Fernández is approved:

_____

_____

_____

Committee Chairperson

University of California, Riverside

Acknowledgments

I would like to thank Dr. David Eastmond for his unwavering support and guidance during my progress towards this degree and as my major adviser. His expertise and know-how made this thesis possible. Even before I entered his research group he has been a genuine champion on my behalf. His door is always open for my ceaseless questions and wonderings. In his research group, I have grown as a scientist, a writer, a thinker, and as a person. For this, I cannot give enough thanks.

I would like to thank the members of my thesis committee, Dr. Carl Cranor and Dr. David Volz for their commitment and flexibility as I have undergone this process. Also, for their unique viewpoints and expertise on the subject matter.

I would like to thank my parents, Ivan and Melissa Fernández for their thoughts and prayers as I have gone through my educational career. They have been vital for my success and a place of comfort. They have supported me as I moved across the country and to other countries in the pursuit of knowledge.

Furthermore, I would also like to thank Hector Godoy for always listening to me and making sure that I did not become too wrapped up in my work. He was always there when I wanted to quit and made sure that I kept my priorities straight. From the trips to the beach and to see snow his friendship has made all the difference. Because of you, I will always keep swimming.

I would like to acknowledge the Lord my God for always seeing me through.

Dedication

I dedicate this thesis to Dr. Deirdre Hill.

You believed in me before I knew what to believe in.

ABSTRACT OF THE THESIS

A Screening-Level Hazard Assessment of Human and Environmental Health Endpoints of Halogenated and Organophosphate Flame Retardants

by

Seth Rojello Fernández

Master of Science, Graduate Program in Environmental Toxicology
University of California, Riverside, March 2019
Dr. David Eastmond, Chairperson

ABSTRACT

Organohalogen flame retardants are extensively used in both industrial and consumer products but now are being phased out of circulation by both state governments and the United States Federal government. Organophosphate flame retardants have been chosen as the replacement for the halogenated flame retardants. However, relatively little is known about the potential hazard of these class of chemicals to cause adverse health and environmental effects. To address this, we conducted a health and environmental hazard screening of 90 halogenated and 97 organophosphate flame retardants based on the GreenScreen® or Quick Chemical Assessment Tool (QCAT©) methodologies. Priority consideration was given to human health hazards including carcinogenicity (including mutagenicity and genetic toxicity), reproductive or developmental toxicity, endocrine disruption, and acute mammalian toxicity. Environmental hazards given priority consideration included acute aquatic toxicity, persistence, and bioaccumulation. Using publicly available information, each hazard category was assigned a concern level (very-low, low, moderate, high, or very high) based on pre-defined numerical ranges,

such as no-observed adverse effect levels and hazard classification schemes from authoritative sources, when available. Where empirical data were not identified, quantitative structure-activity relationship (QSAR) models were relied upon to predict hazard potential. After assigning concern levels for each priority health effect, each chemical received a score, similar to a report card (A, B, C, or F). The majority of the screened chemicals received an F grade due to empirical data suggesting high hazard, QSAR model predictions, and/or excessive data gaps. Acute Mammalian Toxicity was the most prominent potential health hazard identified based on empirical data. The most prevalent data gap was found in both reproductive toxicity and endocrine disruption endpoints due to the lack of identified empirical data or computer models able to predict this hazard. This study highlights the limited toxicity information available for these widely used chemical classes and indicates that more testing and oversight is critically needed to identify safer alternatives for fire prevention.

Table of Contents

List of Figures

Chapter 1

Chapter 2

List of Tables

General Introduction

The Federal Drug and Food Administration regulates food products and medical drugs. In this way, the United States government is proactive in regulating chemical compounds that are allowed into circulation. In regards to consumer products such as sofas, electronics, and baby products, the regulatory system is much more passive or reactive. Commonly, the way a chemical is phased out or limited in its use is after public health has been, or perceived to have been, negatively impacted, which is typically associated with a lack of adequate toxicological testing prior to its use. A notable example of this is the introduction of tris-(2, 3-dibromopropyl) phosphate (tris-BP) into children's pajamas during the 1970s. Tris-BP was thought to be a totally safe and effective flame retardant in these pajamas but was discovered to have mutagenic and potentially carcinogenic effects on children (Blum & Ames, 1977). A year later another member of the tris-family was discovered by the same research group to have potential cancer-causing effects (Gold, Blum, & Ames, 1978). These toxic chemicals were phased out but were replaced with other compounds with unknown toxicities. This trend has continued to this day with flame retardants of various classes such as the halogenated and organophosphate flame retardants. In 2017, the US Consumer Products Safety Commission, after extensive research and with scientific support, decided to grant Petition HP 15-1 to regulate halogenated flame retardants, as a class, in certain consumer products (Consumer Product Safety Commission, 2017). In addition, the California State legislature passed a law banning many halogenated compounds from many consumer

products in 2018 in Assembly Bill 2998 (Bloom & Kalra, 2018). As the halogenated flame retardants have been phased out of circulation, the organophosphate flame retardants are being increasingly used as the replacements. Research has been conducted that has indicated that organophosphate flame retardants are often as toxic as the halogenated flame retardants which they have replaced. This research has only looked at commonly used flame retardants and not chemical classes as a whole (Aschberger, Campia, Pesudo, Radovnikovic, & Reina, 2017).

One reason for the continual replacement of toxic flame retardants with similarly toxic substitutions is due to the reactive system that the United States has for chemicals in consumer products. Commonly, when a compound is phased out of circulation it is replaced by another chemical in the same class which has similar if not identical hazardous toxicological effects. One possible way to address the problem of toxic chemicals in consumer products is to regulate chemicals as a class. If there are non-toxic exceptions within a given class that adequately perform the role then they can be exempted from the class phase out after evidence has accumulated to show that they are non-toxic. It would be better for human and environmental health to be proactive with these judgments than reactive.

This possible solution does come with a problem, which is how to properly assess chemical compounds as a class which can include hundreds of individual compounds. Most chemical assessment tools such as GreenScreen® and Design for the Environment are not only costly and require large amounts of time but would be void by the time the full class could be assessed since a typical assessment is often valid for only

a limited period of time (Anastas, Heine, & Whittaker, 2018; Scr, 2016). In these circumstances, it is recommended that a systematic approach be utilized to efficiently assess patterns of toxicity of chemical compounds, notably flame retardants in current circulation.

The Quick Chemical Assessment Tool (QCAT©) developed by the Washington State Department of Ecology in 2016 was created as an alternative to GreenScreen® and Design for the Environment that could be used by small to medium businesses (Anastas et al., 2018; Stone, 2016). The QCAT© methodology would be used as a first pass assessment to determine general toxicity patterns for a class of flame retardants. Then any compounds that pass the QCAT© assessment could undergo a more thorough assessment using the GreenScreen® or similar approach. It should be noted that both of these approaches focus solely on hazard and do not take into account exposure or risk. To our knowledge, this type of systematic hazard assessment has not previously been attempted on an entire class or classes of chemicals.

Chapter 1 of this thesis will cover the halogen class of flame retardants and an in-depth look at the QCAT© methodology. A report of the raw results and discussion of those results will also be undertaken. Then Chapter 2 will cover the organophosphate class of flame retardants which will be compared to the halogenated flame retardants. Since the organophosphate flame retardants are currently being used to replace halogenated flame retardants it is critical that there is an understanding of both class's toxicities. A discussion of GreenScreen® and next steps will also be presented in Chapter 2. Lastly, a general conclusion which will summarize the results of both chapters and

lasting conclusions that were made by the juxtaposition of the patterns of toxicity of these two classes will be made.

Chapter 1

A Screening-Level Hazard Assessment of Human and Environmental Health Endpoints of Halogenated Flame Retardants

Introduction

Flame retardants are common additives in many consumer products such as in electronics, building insulation, polyurethane foam, and wire/cables (Blum, Daley, & Babrauskas, 2011). In recent years, there have been increasing concerns about their potential human health effects and that, in certain situations, these additives may be doing more harm than good. There are two main classes of flame retardants used throughout the industrialized world: the organohalogen (OHFR), the focus of this article, and the organophosphate flame retardants (OPFR).

OHFR are notably used in polyurethane foam and have been commonly used in couches, pillows, mattresses, and other cushioned household items (Stapleton et al., 2011). These flame retardant chemicals are not covalently bound to the foam, which results in high bioavailability of the OHFR in indoor environments, particularly in dust (Wu & Yang, 2006). Because some OHFR is semi-volatile, they can also sorb onto indoor surfaces, which can subsequently become a significant source of exposure. It is through dust that infants, children, and adults, as well as pets, are primarily exposed (Cequier et al., 2014; de Boer, Ballesteros-Gómez, Leslie, Brandsma, & Leonards, 2016; van I & de, 2012). Recent studies have shown that infants and children are exposed to OHFR-contaminated dust at elevated levels, largely due to more hand to mouth activity (Larsson et al., 2018; Xu et al., 2016). In recent years, relatively high concentrations of OHFR have been found in vegetables, fish, and bodily fluids, with some of the highest levels being found in household pets and residents of California, where stringent flame retardant standards for furniture have resulted in increased exposure rates (Cooper et al.,

2016; Cordner, Mulcahy, & Brown, 2013; The & European Union, 2003; Zota et al., 2011).

The OHFR class is comprised of brominated, chlorinated, and fluorinated compounds. For some specific flame retardants such as the polybrominated diphenyl ethers (PBDEs), a large number of toxicological studies have been conducted (Lignell et al., 2016; Stapleton et al., 2009; Zota et al., 2011) whereas for others very little is known about their toxicity and environmental effects. Some flame retardants such as tris(1,3-dichloro-2-propyl) phosphate (TDCPP) and 1-propanol, 2,3-dibromo-, 1,1',1"-phosphate (TDBPP) have been shown to be mutagenic in bacteria, and possibly carcinogenic in rodents (Gold, Blum, & Ames, 1978). Others such as Tris (2-chloroethyl) phosphate [aka ethanol, 2-chloro-, phosphate] (TCEP) and Mirex have exhibited reproductive, developmental and/or other toxic effects (e.g. neurotoxicity), and are included in the present evaluation for comparative purposes. Similarly, other OHFR such as phenol, 4, 4'-(-methylethylidene) bis [2, 6-dibromo-] (TBBPA) and hexabromobenzene are profiled in the present assessment due to concerns of acute toxicity to aquatic species. These and other flame retardants have lipophilic properties that facilitate bioaccumulation in the environment (Aschberger, Campia, Pesudo, Radovnikovic, & Reina, 2017; de Boer et al., 2016).

Due to environmental and human health concerns, a few OHFRs have been withdrawn from the market (Commission, 2013; The European Parliament and the Council of the European Union, 2003). In addition, legislative action or other regulatory decisions have resulted in restricted use of some OHFRs. For example, in 2013

California State Assembly Bill No. 127 effectively lowered the high-volume usage of flame retardants in building insulation (October & October, 2015). Also, that same year the governor of California approved a revision of TB117 (TB117-2013) which lowered the amount of potentially toxic flame retardants in furniture and baby products (Blum et al., 2011; "Department of Consumer Affairs Technical Bulletin 117-2013," 2013).

However, the restricted OHFRs are often replaced by similar chemicals for which little is known about their potential adverse effects. These replacements frequently come from the same or another related class of chemicals resulting in similar hazardous effects as the original compound. There is a critical need to be able to quickly evaluate multiple adverse health and environmental effects for a range of chemicals to allow manufacturers and regulators to replace flame retardants and other hazardous chemicals with less toxic and safer alternatives. Ideally, one would be able to efficiently assess entire classes of chemicals so that risk managers can quickly identify the most non-toxic chemicals and proactively reduce hazardous exposures.

The lack of information on potentially hazardous effects generally stems from a lack of key toxicological studies on many flame retardants and their related conjugates and metabolites. In some cases, the critical studies have been conducted but the information is not in the public domain or has not been accessible. In recent years, a large number of databases have been created to make chemical and toxicological information more readily available to the public. Evaluation of chemicals is generally conducted on a chemical-by-chemical basis or by examining one type of effect across a range of compounds. To date, it has been difficult to evaluate an entire class of chemicals across a range of environmental

and health endpoints. To our knowledge, there have been few if any systematic assessments previously performed on entire classes of chemicals.

Hazard Screening Methodology

Recently, a variety of strategies have been developed to screen chemicals to identify and rank toxicity, environmental effects, and related properties as well as to identify existing gaps in knowledge (European Chemicals Agency, 2015; IARC, 2010; US EPA, 2014). Traditionally these rankings have focused on evaluating specific hazard or environmental effects, such as acute aquatic toxicity or carcinogenicity. More recently, more comprehensive approaches have been created which evaluate and summarize multiple types of effects and chemical properties. For example, the US EPA's Design for the Environment (DfE) is an approach that has been developed in recent years to identify safer products through an evaluation of their chemical ingredients (US EPA, 2018d). Another, hazard assessment and decision-assisting method, called GreenScreen® for Safer Chemicals (GreenScreen®), has been developed to assist those involved in product design, manufacture, purchasing and regulation to manage chemical risk by identifying chemicals of concern within products and to allow safer alternatives to be selected (Lavoie et al., 2010); http://www.cleanproduction.org/GreenScreen®.php). In the GreenScreen® approach™, 18 hazard endpoints are evaluated covering a broad range of toxic and environmental effects. The resulting hazard classification of each endpoint is compared with a series of benchmarks to classify the hazard and eventually result in an overall assessment. Because the GreenScreen® approach has high data requirements and

requires considerable technical expertise, its use for assessing chemicals with modest amounts of information such as the flame retardants has been limited. A simpler and less demanding screening approach known as Quick Chemical Assessment Tool (QCAT©) has been developed by the Washington State Department of Ecology (Stone, 2016). This method focuses on a smaller set of hazard endpoints and, as a result, has fewer data requirements. While simpler and more practical in many circumstances, this also means that certain types of toxic effects (e.g. neurotoxicity, skin sensitization, eye irritation, etc.) will not be detected or evaluated. In the QCAT© approach, chemicals are ranked for each of 6 human health-related endpoints plus persistence, bioaccumulation, and acute aquatic toxicity, resulting in an evaluation of very-high, high, medium, low, very-low hazard, or data gap for each endpoint. The individual endpoint evaluations are combined into an overall initial, and then, final grade. The primary objective of this study was to apply the QCAT© method to conduct a screening-level assessment of health and environmental hazard endpoints for 90 OHFRs, and to present the results so that the effects and evaluations of the chemicals in this class can be easily viewed and compared. Because this is the first time that the QCAT© approach has been used to assess a large group and class of chemicals, additional details on the methods and the origins of the results have been included.

Materials and Methods

QCAT© Method

The QCAT© method is described in detail elsewhere (Anastas, Heine, & Whittaker, 2018; Stone, 2016) and as a result, is only briefly described below. As illustrated in Figure 1, the QCAT© process starts with generating a list of compounds of interest. After that list is compiled with compound name and CAS number, then data acquisition can occur. One compound and one endpoint are investigated at a time until data has been obtained for all 9 endpoints for the chemical of interest. The first data sources that are examined are Step 1 (authoritative) sources, which if found for the endpoint of interest, will satisfy the data requirement and additional Step 2 (less authoritative) sources are not considered. If there is not a Step 1 source then the evaluation proceeds using Step 2 sources of empirical or other relevant information. For these, two data points are needed. If there are no Step 1 or Step 2 sources, then a QSAR prediction can be used. This approach relies primarily on authoritative sources and that an in-depth literature review for each chemical is not undertaken as part of the QCAT© assessment. After every endpoint has a hazard score, an initial grade is assigned. If there are data gaps, then the compound will undergo a "Data Gap Analysis." If there are no data gaps or after the analysis has been conducted, the final Benchmark grade is assigned. The next compound of interest will then be evaluated until all of the chemicals have been completed. Additional details on specific steps in the process are described below.

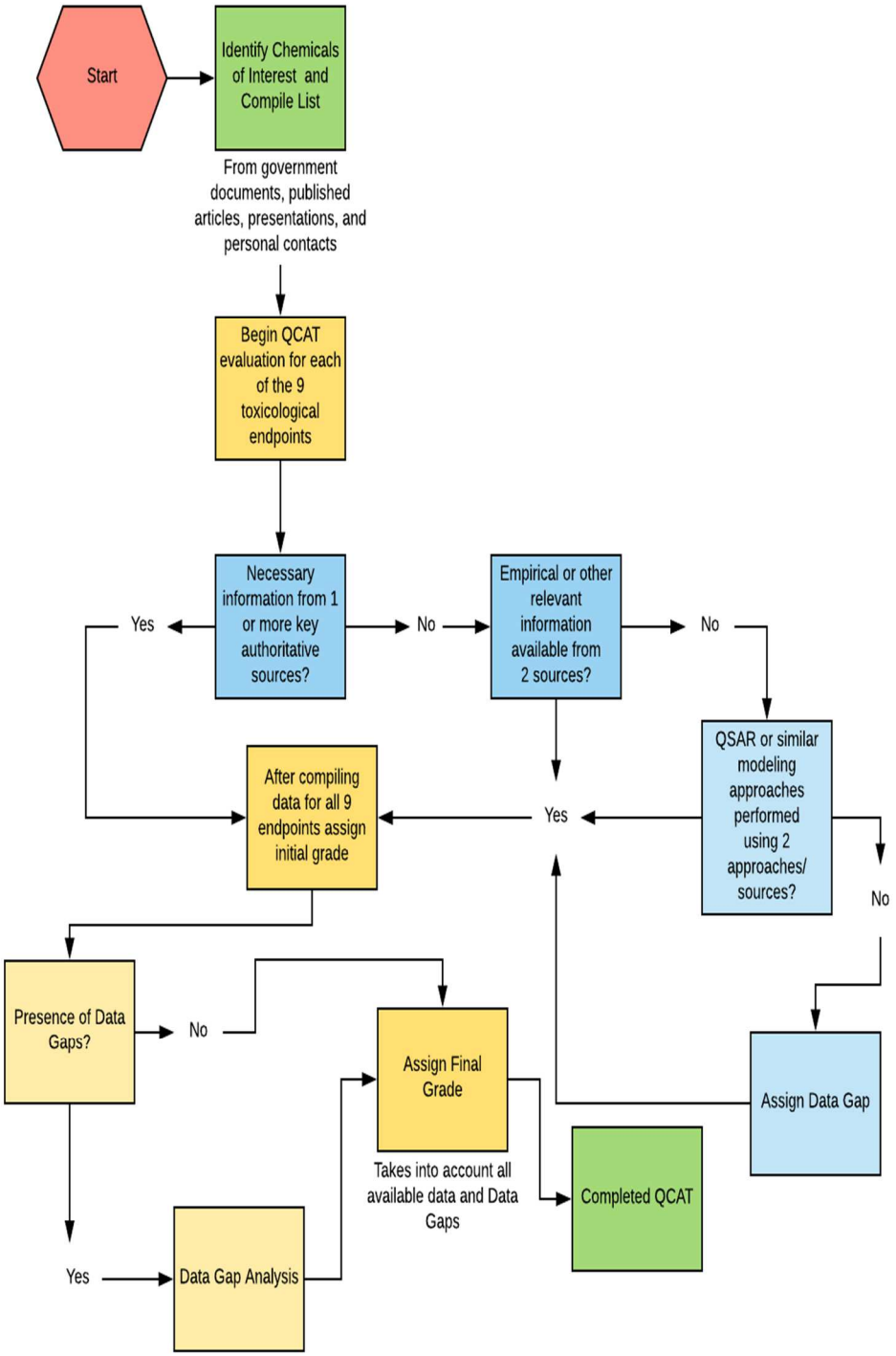


Figure 1 QCAT© Process

Flame Retardant / Compounds of Interest List

A list of common use flame retardants was compiled from multiple sources including previously published data, a high commercial use list, non-governmental organizations, and web searches. This resulted in a final list of 90 halogenated flame retardants. The complete list with CAS registry numbers and full names can be found in Appendix 1.

Hazard Categories

As introduced above, the QCAT© prioritizes six human health hazards, acute mammalian toxicity, carcinogenicity, reproductive toxicity, developmental toxicity, mutagenicity/genetic toxicity, and endocrine disruption and the three priority environmental hazards, acute aquatic toxicity, persistence, and bioaccumulation (See Table 1). These hazard endpoints were included since they were considered to pose the greatest threat to sensitive populations such as children and to provide a good indication of the risks posed by chemicals (Stone, 2016).

Human Health Endpoint	**Environmental Health Endpoint**
Acute Mammalian Toxicity (AT)	*Acute Aquatic Toxicity (AA)*
Carcinogenicity (C)	*Persistence (P)*
Reproductive Toxicity (R)	*Bioaccumulation (B)*
Developmental Toxicity (D)	
Mutagenicity/Genetic Toxicity (M)	
Endocrine Disruption (E)	

Table 1 QCAT© Endpoints

Public Database Searches for Toxicity Data

Chemical Abstract Services (CAS) registry numbers served as the primary identifier for the 90 brominated, chlorinated, or fluorinated flame retardants screened in the present assessment. All compounds of interest were required to have a CAS number. In addition, for some compounds, a Simplified Molecular Input Entry System (SMILE) Notation was also identified for use in modeling software. This SMILE notation was retrieved from ChemIDplus, PubMed, or the PubChem Sketcher tool (NCBI, 2018; U.S. National Library of Medicine, 2018). Due to the limited identified peer-reviewed toxicity data in public databases such as PubMed and ToxNet, other information sources, which included non-peer reviewed information or unpublished data were also searched. For a number of chemicals (as noted in Appendix 2), previously performed hazard screens or toxicity reviews were used to assign hazard scores when these could be identified, such as those conducted by the:

- U.S. EPA Design for the Environment program (DfE)(US Environmental Protection Agency, 2018d),
- European Chemicals Agency database (Union, 2018),
- TEDX (Ted.com, 2018),
- Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency/Prop 65 (OEHHA, 2018),
- International Agency for Research on Cancer,
- Deutsch Mak list (Deutsche & Forschungsgemeinschaft, 2018),
- OSPAR rating (Safer Chemicals Database, 2018),

- San Antonio Statement on Brominated and Chlorinated Flame Retardants,
- Health Canada/Canadian Environmental Protection Agency (*Canadian Substances Registry (DSL)*, 2018).

Many of these existing hazard sources were acquired using open-access public databases, either by using CAS registry number or SMILE notation. These databases included: ChemHat, ChemView, ChemIDplus, and PubMed. If a DfE had been conducted by the US EPA, it was used in place of Step 1 and Step 2 sources. DfE normally gives empirical data associated with the grade given for each endpoint (US EPA, 2018d). It also covers all endpoints associated with both GreenScreen® and QCAT© methodologies except endocrine disruption. For a full list of databases used and the QCAT© flow chart, see Chapter 2 Appendix 1 and 3).

Modeling Software

For several of the human health and environmental endpoints, modeling software was used to predict toxicity values and hazard scores. These software platforms are open access and publicly available. However, they do require some technical knowledge and an understanding of both CAS Registry Numbers and SMILE notations to perform. The following software was used to predict the associated endpoint when authoritative sources or empirical data were not available:

- Epi-Suite: Persistence, Bioaccumulation
- U.S. EPA T.E.S.T: Acute Toxicity, Developmental Toxicity, Mutagenicity, Acute Aquatic Toxicity, Bioaccumulation

- Vega (various models): Mutagenicity, Carcinogenicity, Developmental Toxicity, Reproductive Toxicity, Estrogen/Endocrine Disruption, Persistence, Bioaccumulation

Predictions generated from "Read-Across" approaches were not used in assigning a grade for the chemical being evaluated. If the only data that were available were from "Read-Across" approaches, a designation of "Data Gap" was given (See Chapter 2, Appendix 3 for the full list of software used).

Assigning Initial Grades

Initial grades were assigned to each individual endpoint using a scale from "very low" to "very-high" depending on the endpoint in question. If no information was found, then a designation of "data gap" was given (Stone, 2016). The hazard scores were then compiled into an Initial Grade, independent of any data gaps that might be present. The data acquired determined the score given. The QCAT© guidance contains instructions on how each endpoint is to be graded (Stone, 2016). For example, if the Acute Toxicity endpoint had data that indicated that the oral LD50 was ≤ 50 mg/kg bw, then a hazard score of very-High was given, or if data showed that, for the same endpoint, an Inhalation LC50 > 20,000 ppm, then a grade of Low was given. The QCAT© approach also separates Step 1 sources, such as ECHA's GHS Statements, which only require one data entry to assign a grade, and Step 2 sources, which are more technical in nature and require two data entries for a grade to be assigned. The only exception to this rule is if there is reliable information from one Step 2 source, a hazard score can be assigned, but it

must be notated in the data set and explained in the final report on that chemical (Stone, 2016). For example, Hazardous Substances Data Bank (HSDB) would be considered to be a Step 2 source since it requires a trained professional to interpret the empirical data and be used to assign a hazard score alone with proper notation. If information was found from a Step 1 source, there is no need to continue to evaluate Step 2 sources. In this evaluation, if no Step 1 data was available and empirical data was found, the empirical data were given priority in the evaluation over other predicted or modeled data types. After Step 1 and Step 2 sources had been acquired, an Initial Grade was given based on all known data.

Assigning Final Grades / Benchmark Scores

After initial concern levels such as Low, Moderate, or High were given for each hazard category, a final grade (i.e. Benchmark score) was assigned based on established QCAT© criteria similar to an academic report card with grades of A, B, C, or F. The QCAT© grading process is based upon similar processes established for the GreenScreen® with the main difference being that the amount of information used to assign a QCAT© score is substantially less than that required for a GreenScreen® assignment.

Outlined below are modifications/clarifications to the standard QCAT© and GreenScreen® guidance documents which were made to account for the overall limited quantity of data identified. The main modification involved the application of quantitative structure-activity relationship (QSAR) models when the prescribed empirical data were

not identified. Although the guidelines currently allow for QSAR, particularly for human health endpoints, use of QSAR for environmental health endpoints is less explicit within the QCAT© and GreenScreen® guidance. This tended to allow for higher initial grades (A-C) for many flame retardants, which ultimately received a Benchmark Score of F once QSAR and data gaps were considered. There was not a single occurrence where the OHFR was given a higher Benchmark Score once QSAR and data gaps were considered. The main difference between the Initial Grade and the Benchmark Grade was the inclusion of data gaps into the Benchmark grade.

The QCAT© methodology details how to assign the Benchmark grades depending on the individual endpoint scores. In addition, there is available on the QCAT© website a "Grading Tool" using an Excel™ worksheet which we used to check the assigned Benchmark Score, and to perform a "Data Gap Analysis"; In all cases, use of the spreadsheet agreed with our manual grade determinations (Stone, 2016).

The present assessment also did not consider potential hazards posed from end-use specific chemical transformation products since these are largely unknown. Similarly, surrogate or analog approaches were not used to fill data gaps due to the overall similarity in chemical structures and lack of clearly defined delineation strategies based on structural attributes. As indicated above, the QCAT© is a screen and not a comprehensive evaluation of potential hazards posed by chemical alternatives as is the GreenScreen® approach. It is, however, much more time efficient and requires less technical expertise. However, if a chemical is found to be a poor alternative using the QCAT© methodology, it will also be a poor candidate when using the GreenScreen®

method. A chemical that is not rejected by QCAT© may still prove to be unsatisfactory if a more complete review is done using the GreenScreen® or similar method.

Results

The following section details the results of the QCAT© assessment by endpoint. Figure 2 shows a heat map of all the endpoints and their hazard scores for each compound assessed with very-Low in dark green, Low in light green, Moderate in yellow, High in red, and very-High in maroon. The heat map clearly shows consistent very-High hazard scores for the Persistence endpoint. It also shows an abundance of High to very-High hazard scores for the Bioaccumulation endpoint. For Carcinogenicity and Development toxicity, Moderate hazard scores predominate. The 14 compounds previously assessed by DfE kept their DfE scores with the exception of Endocrine Disruption which is not evaluated in the DfE approach. To see the full QCAT© data associated with this class of compounds see the link provided in Appendix 4. Patterns for the individual endpoints are described in more detail below.

Halogenated Flame Retardant
Heat Map

CAS #	Initial	Final	AT	C	R	D	M	E	AA	P	B
1084889-51-9	C	C	H	M	M	M	L	M	L	vH	L
1163-19-5	F	F	L	M	L	H	L	M	L	vH	H
118-79-6	F	F	H	M	H	M	L	H	vH	vH	vH
168434-45-5	C	C	M	L	dg	L	L	dg	L	vH	vL
23488-38-2	F	F	L	M	M	L	L	H	vH	vH	vH
25713-60-4	C	C	L	L	L	L	L	dg	M	vH	H
31780-26-4	C	C	M	M	M	M	L	M	M	vH	L
31977-87-4	C	C	M	L	dg	M	L	dg	L	vH	L
32534-81-9	F	F	L	M	M	H	L	H	vH	vH	vH
32536-52-0	F	F	L	M	H	H	L	H	vH	vH	vH
32588-76-4	F	F	L	M;	L;	L	L	H	L	vH	vH
3278-89-5	F	F	L	L	dg	M	L	H	vH	vH	vH
33798-02-6	F	F	H	M	M	M	M	H	H	vH	vH
34571-16-9	C	C	M	M	M	L	L	M	L	vH	L
35109-60-5	F	F	M	M	dg	M	M	vH	L	vH	vH
3555-11-1	F	F	M	L	M	M	L	M	L	vH	vH
37853-59-1	F	F	L	M	L	L	L	H	H	vH	H
38521-51-6	F	F	M	M	dg	M	M	H	vH	vH	vH
39569-21-6	F	F	M	M	M	M	L	M	H	vH	vH
39635-79-5	C	C	H	L	M	M	L	M	L	vH	H
42757-55-1	C	C	M	M	dg	M	M	dg	L	vH	M
497107-13-8	C	C	M	L	dg	M	L	dg	L	vH	vL
52434-90-9	F	F	M	M	M	M	M	H	L	vH	vH
57829-89-7	F	F	L	M	dg	M	L	dg	M	vH	H
58495-09-3	F	F	M	M	dg	M	M	dg	vH	vH	vH
58965-66-5	F	F	L	L	L	M	M	H	L	vH	vH
59447-55-1	F	F	M	M	dg	M	M	H	H	vH	vH
608-71-9	F	F	H	M	M	L	L	H	vH	vH	H
615-58-7	F	F	vH	M	M	M	L	H	H	vH	vH
68928-70-1	F	F	L	L	L	L	M;	H	L	vH	L
70156-79-5	F	F	M	L	M	M	L	M	L	vH	vH
72625-95-7	F	F	H	L	dg	L	M	dg	L	vH	H
84852-53-9	F	F	L	M	L	L	L	H	L	vH	vH
85-22-3	F	F	L	M	M	M	L	H	L	vH	vH
855992-98-2	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
855993-01-0	F	F	M	L	dg	M	L	dg	L	vH	M
87-82-1	F	F	M	M	M	L	L	H	vH	vH	H
87-83-2	F	F	H	M	M	L	L	H	vH	vH	vH
135229-48-0	B	B	L	L	L	L	L	dg	L	vH	L
148993-99-1	F	F	dg	dg	dg	dg	dg	H	dg	dg	dg
59447-57-3	F	F	L	L	L	L	M	H	L	vH	vH
88497-56-7	B	B	L	L	L	L	L	dg	L	vH	L
126-72-7	F	F	H	H	H	M	H	H	vH	vH	vH
19186-97-1	F	F	L	M	L	H	M	H	L	H	H
632-79-1	F	F	M	L	M	M	L	H	H	vH	H
82001-21-6	C	C	M	M	L	M	M	dg	L;	vH	vL
90075-91-5	F	F	H	L	dg	M	M	dg	vH	vH	vL
183658-27-7	F	F	L	M	M	M	L	H	M	vH	vH
20566-35-2	F	F	vH	M	M	M	L	H	M	H	L
26040-51-7	F	F	L	M	M	L	M	H	vH	vH	vH
75795-16-3	F	F	M	M	H	M	M	H	M	vH	vH
77098-07-8	F	F	M	M	dg	M	M	H	M	vH	vH
115-96-8	F	F	M	H	H	H	vH	L	H	vH	vH
13674-84-5	F	F	H	H	H	H	M	H	M	vH	H
13674-87-8	F	F	H	H	M	M	M	H	H	vH	H
38051-10-4	F	F	L	M	M	M	M	H	M	vH	H
66108-37-0	F	F	M	M	dg	M	M	dg	M	vH	vH
78-43-3	F	F	H	M	M	M	H	H	M	vH	vH
25495-98-1	F	F	vH	M	M	M	M	H	H	vH	vH
25637-99-4	F	F	L	M	H	H	L	H	H	vH	vH
3194-55-6	F	F	L	M	H	H	L	H	vH	vH	vH
3194-57-8	F	F	L	M	M	L	L	H	vH	vH	H
3322-93-8	F	F	L	M	M	M	H	H	L	vH	vH
115-27-5	F	F	M	H	M	M	M	dg	M	vH	H
115-28-6	F	F	M	H	M	M	M	L	M	vH	vL
13560-89-9	C	C	H	M	L	L	L	M	L	vH	H
2385-85-5	F	F	vH	H	H	H	L	H	vH	vH	vH
5436-43-1	F	F	M	M	H	H	M	H	H	vH	vH
51936-55-1	F	F	L	M	M	M	L	H	M	vH	H
1522-92-5			L	M	M	M	H	M	M	vH	vL
3296-90-0	F	F	M	H	M	M	H	H	M	H	H
36483-57-5	F	F	L	M	M	L	M	M	vH	vH	L
191680-81-6	F	F	L	M	H	H	L	dg	H	vH	H
85535-84-8	F	F	L	H	M	M;	L	H	vH	vH	vH
85535-85-9	F	F	L	H	H	H	M	H	vH	vH	H
117-08-8	C	C	L	M	L	L	M	M	L	vH	M
13560-92-4	F	F	vH	M	dg	M	L	dg	L	vH	vH
21850-44-2	F	F	L	M	M	M	M	H	L	vH	H
25327-89-3	F	F	L	L	M	M	L	M	H	vH	vH
3072-84-2	C	C	H	M		M	M	M	M	vH	H
37419-42-4	C	C	M	M	dg	M	M	dg	L	vH	H
37853-61-5	F	F	vH	M	M	H	L	M	vH	vH	H
4162-45-2	F	F	H	L	M	M	M	H	vH	vH	vH
55205-38-4	C	C	M	L	M	L	M	M	L	H	H
66710-97-2	C	C	M	L	M	M	M	M	L	vH	H
79-94-7	F	F	L	M	M	H	L	H	vH	vH	vH
134237-52-8	F	F	L	M	H	M	L	H	vH	vH	vH
34237-50-6	F	F	L	M	H	M	dg	H	H	vH	vH
34237-51-7	F	F	L	M	H	M	dg	H	H	vH	vH

Figure 2 Halogen Flame Retardants Heat Map

Acute Mammalian Toxicity

The hazard scores for Acute Toxicity ranged from Low to very-High. Seventy-five percent of the assessed OHFR received a Low or Moderate hazard score in our evaluation (See Figure 3 and Table 2). There were a small number of flame retardants ranked very-High for this endpoint. Generally, the Low hazard scores were assigned based on empirical and authoritative sources while the Moderate hazard scores were based on predictive data.

Acute Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	2					2
vL						
L		14	8	16	13	38
M		6	21	3		30
H		3	7	4	1	14
vH		1	3	2		6
Total	2	24	39	25	14	90

Table 2 Acute Mammalian Toxicity Data

As indicated in the methods section, preference was given to empirical LD50 values, with the lowest LD50 value serving as the basis for the hazard score when Step 1 data were unavailable. As specified in the QCAT© guidance, these determinations were based only rat and human studies, even when studies of other species were available. More empirical data were available for acute toxicity than for the other priority human health categories. As seen in Table 2, 24 OHFR received grades based on the empirical data when Step 1 sources were not found.

When Step 1 and Step 2 sources could not be found, then modeling software such as the U.S. EPA (US EPA, 2018) Toxicity Estimation Software Tool (T.E.S.T.), was used to

predict oral LD50 values in rats. Of the 39 flame retardants that were evaluated by the modeling software, the majority, 21 compounds, where given a Moderate score based on their predicted rat oral LD50 values. Among the remaining OHFR, 7 were rated as High and 3 OHFR rated as very-High. These earned failing Benchmark Scores.

In our evaluation, 6 flame retardants received a very-High hazard score based mainly on authoritative sources and prediction data. Interestingly, it is possible for a flame retardant to receive a High or very-High hazard score for the Acute Toxicity endpoint but still receive a Benchmark score of C (CAS 39635-79-5, 13560-89-9, 3072-84-2)(See Figure 2).

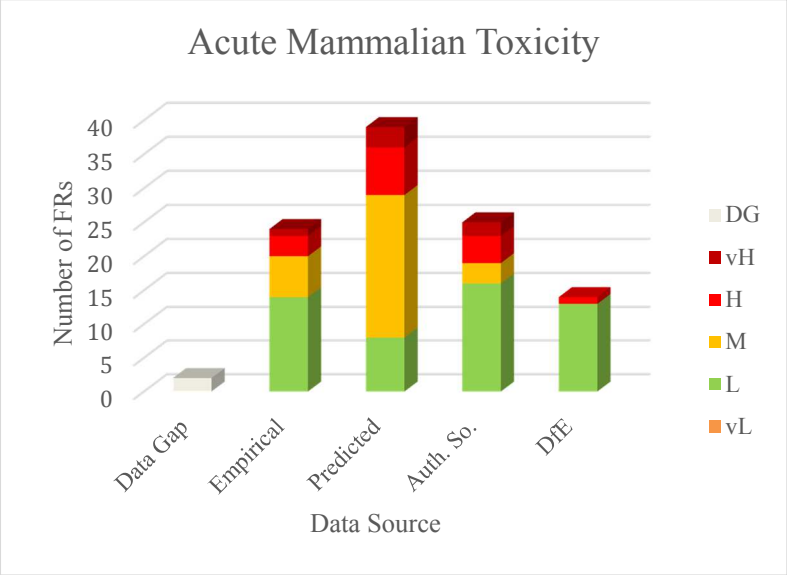


Figure 3 Acute Mammalian Toxicity Data

Carcinogenicity

For carcinogenicity, over sixty percent of all compounds assessed receiving a Moderate hazard score (See Figure 4 and Table 3). Almost all of the compounds evaluated (~65%) received hazard scores from prediction data. Low hazard scores were also assigned to 21 compounds, also mainly from predictive data sources.

Carcinogenicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	2					2
L			16	5	5	21
M		3	41	12	8	56
H			2	9	1	11
vH						
Total	2	3	59	26	14	90

Table 2 Carcinogenicity Data

The hazard score for carcinogenicity relied primarily on prediction scores and lists form authoritative sources rather than numerical ranges, such as those described for acute mammalian toxicity. The designated authoritative sources for carcinogenesis include California Prop 65 list, Deutsch Mak List, and US 14th Report on Carcinogens (Deutsche & Forschungsgemeinschaft, 2018; National Toxicology Program, 2016; OEHHA, 2018). Authoritative sources accounted for 26 hazard scores, most of which received scores of Moderate. Of the 3 OHFRs that had rodent cancer bioassay data (empirical data), all 3 resulted in a Moderate concern designation (Table 3). The 9 compounds that were found on California's Prop 65 list, all received a High hazard score. Almost, thirty percent of compounds received a grade from authoritative sources. Of note, most sources did not have data on the non-linear and more complex halogenated flame retardants.

Since most of the screened OHFR did not have empirical carcinogenicity data, the ISS, Caesar, and Oncologic QSAR models (OECD.org, 2018; Vegahub.eu, 2017) were

used to predict toxicity and identify structural alerts (SA) for carcinogenicity for the remaining 59 flame retardants. If an SA was identified, a hazard score of Moderate was assigned. Some chemicals had more than one SA and the most commonly identified SAs included:

- halogenated aromatic,
- aliphatic halogen,
- epoxides and aziridines, and
- alkyl (C<5) or benzyl esters of sulphonic or phosphonic acid.

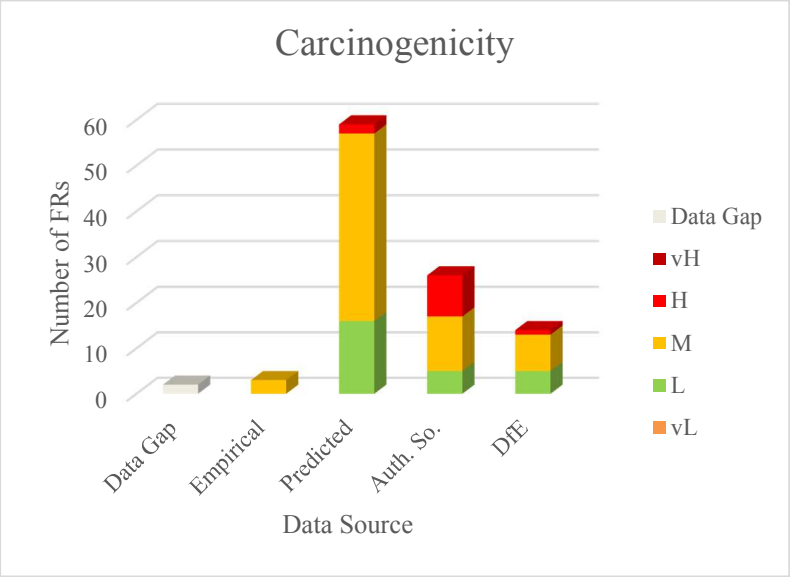


Figure 4 Carcinogenicity Data

Mutagenicity/Genetic Toxicity

The hazard scores for Mutagenicity/Genetic Toxicity tended to be Low to Moderate with a skew towards Low (See Figure 5 and Table 4). Forty-six compounds received a Low score and 34 a Moderate score. These scores relied primarily on predicted data.

Mutagenicity/Genetic Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	4					4
vL						
L		12	23	11	8	46
M		7	23	4	4	34
H		3		2		5
vH				1		1
Total	4	22	46	18	12	90

Table 3 Mutagenicity/Genetic Toxicity Data

The most common, identified data was derived from *Salmonella* reverse mutation assays and often served as the basis of the overall hazard score. A few chemicals were negative in *Salmonella* assays but positive in other assays of genetic toxicity. In these cases, a hazard score of Moderate was applied and the chemicals were included in the empirical source category. When mutagenicity data were not identified, the ISS, Caesar, and other QSAR models (OECD.org, 2018; Vegahub.eu, 2017) were used to identify molecular functional groups or substructures considered to be structural alerts (SA) for *in vivo* or *in vitro* mutagenicity. If an SA was identified, a hazard score of Moderate was assigned. The most commonly identified SAs for mutagenicity included:

- H-bond acceptor,
- 1-phenoxybenzene,
- Alkyl (C<5) or benzyl esters of sulphonic or phosphonic acid, and
- Aliphatic halogen

Less common SAs included “oxolane (tetrahydrofuran) moiety” identified for CAS# 31107-44-5 and “epoxides and aziridines” identified for CAS# 3072-84-2.

Hazard scores for 40 compounds were derived from empirical data, authoritative sources, and/or DfE assessments. Out of these 40 compounds, 12 were given a hazard score from DfE.

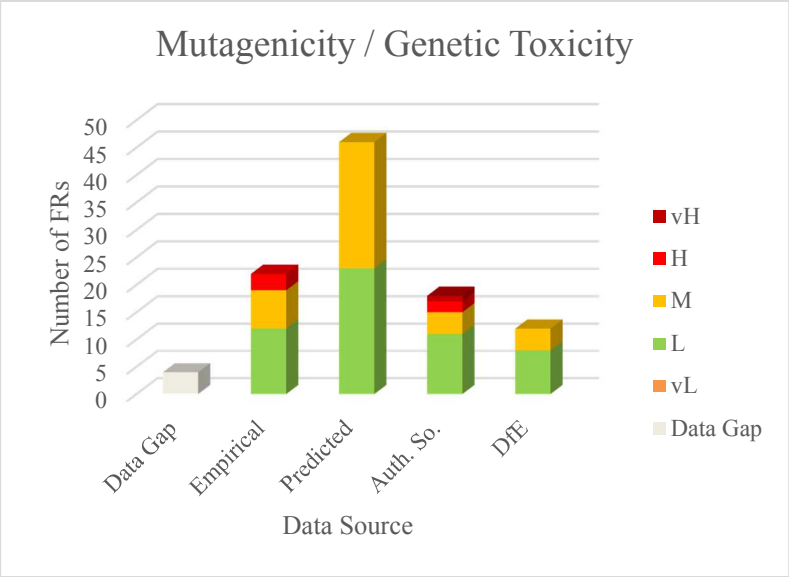


Figure 5 Mutagenicity/Genetic Toxicity Data

Reproductive/Developmental Toxicity

The general outcome seen for the Reproductive and Developmental Toxicity endpoints is Moderate hazard which was seen with 39 and 52 compounds of the compounds, respectively (See Figure 6,7 and Table 5,6). Prediction software was largely used to designate these hazard scores.

Reproductive Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	20					20
L		3	2	10	10	15
M		4	29	6	3	39
H			1	15	1	16
vH						
Total	20	7	32	31	14	90

Table 4 Reproductive Toxicity Data

Developmental Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	2					2
vL						
L		3	10	8	8	21
M		11	35	6	2	52
H		5	2	8	4	15
vH						
Total	2	19	47	22	14	90

Table 5 Developmental Toxicity Data

For Reproductive Toxicity, 32 OHFR were classified based on predictions while 31 were determined based on information from authoritative sources. For Developmental Toxicity, the majority of flame retardants were classified according to predictions (47 OHFR), with 19 based on empirical data and 22 based on authoritative listings.

For OHFR which were not listed or classified as reproductive or developmental toxicants by an authoritative source, concern levels were assigned based on NOAEL values identified from rodent two-generation reproduction or developmental toxicity

studies. According to the QCAT© methodology for Reproductive Toxicity, a grade designation can be made based upon LOAEL, TD_{lo}, or TC_{lo} values. However, there is no way described to make a grade designation for Developmental Toxicity from empirical data. As a result, the evaluator is given considerable latitude to estimate a grade based on LOAEL or NOAEL values.

There were also gaps in the assessment. The majority of reproductive studies focused on either males or females and did not include both. Many developmental studies relied upon initial birth weights and did not include longitudinal developmental studies. It should be noted that there may be other gaps in this area as some of the designated prediction software such as the US EPA's T.E.S.T. makes predictions for Developmental Toxicity but not for Reproductive toxicity. As a result, there were 20 data gaps for the Reproductive Toxicity endpoint, the largest number among the assessed flame retardants. Since there is little empirical data to support Reproductive and Developmental Toxicity, a single data point may have been used to determine the initial and final score using Step 2 sources.

Both endpoints saw a higher percentage of High hazard scores according to authoritative sources while the software predictions gave a majority of flame retardants a Moderate hazard score. This discrepancy between the two sources warrants further investigation.

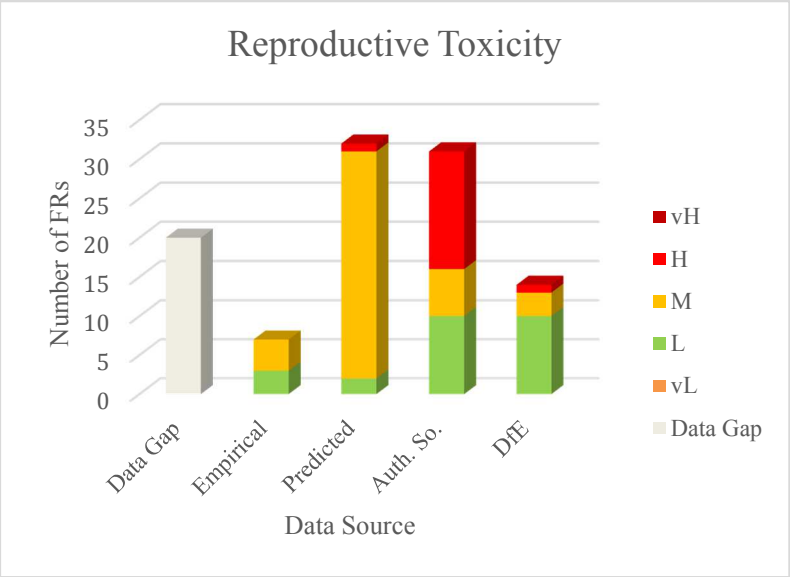


Figure 6 Reproductive Toxicity Data

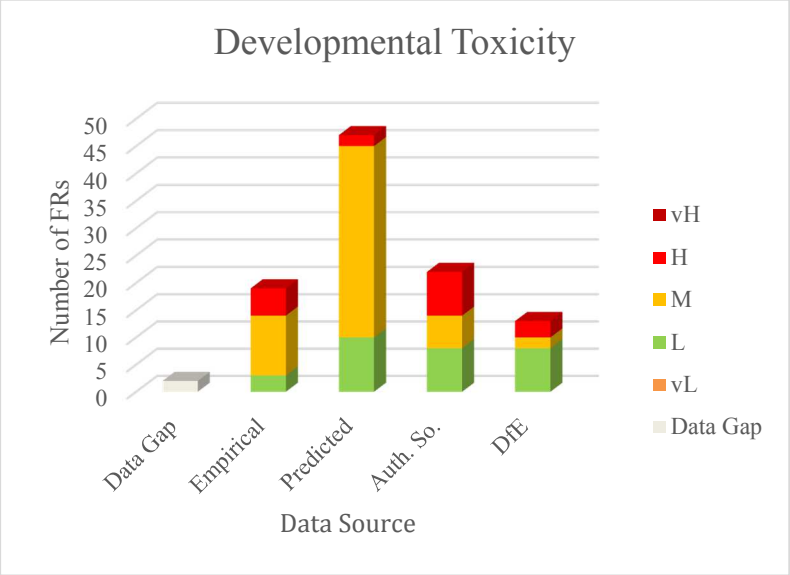


Figure 7 Developmental Toxicity Data

Endocrine Disruption

The Endocrine Disruption endpoint was identified as a High hazard property with 53 compounds (almost 60%) given a High score from authoritative sources (See Figure 8 and Table 7).

Endocrine Disruption	*DGap*	*Empirical*	*Predicted*	*Other*	*DfE*	*Total*
DGap	18					18
vL						
L		1		1		2
M			14	3		17
H				53		53
vH						
Total	18	1	14	57		90

Table 6 Endocrine Disruption Data

The recommended prediction models cover only a subset of the endocrine disruption pathways. For example, Vega QSAR models provide two ways to predict endocrine disruption, Estrogen Receptor Relative Binding Affinity model (IRFMN) and Estrogen Receptor-mediated effect (IRFMN/CERAPP) (Vegahub.eu, 2017), but do not cover other pathways. Use of the Vega model resulted in predictions for an additional 14 flame retardants which all received Moderate hazard scores.

Only 1 OHFR had empirical data to designate a hazard score (CAS 115-96-8). CAS 115-28-6 was the only OHFR that received a hazard score of Low which was due to a designation by an authoritative source. Endocrine Disruption had the second highest amount of data gaps with a total of 18.

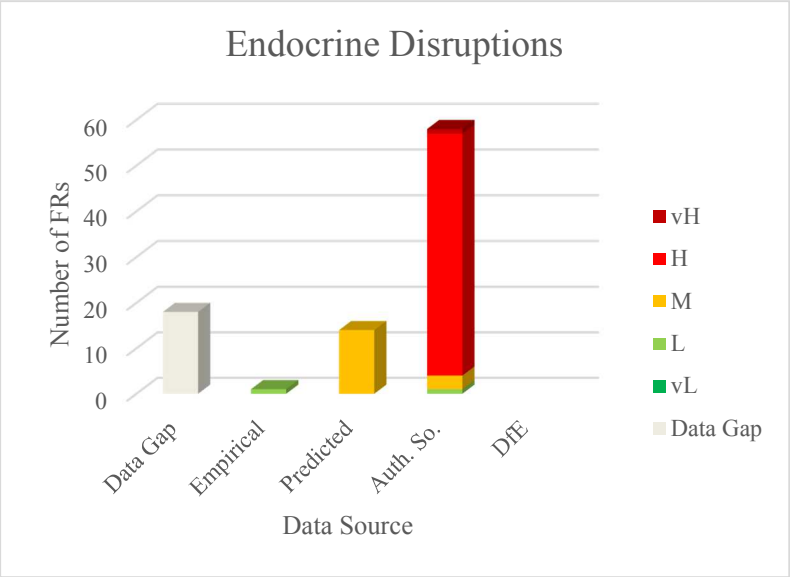


Figure 8 Endocrine Disruption Data

Acute Aquatic Toxicity

In general, the OHRF were scored as Low to Moderate for Acute Aquatic Toxicity with 42 scored as Low and 18 compounds scored Moderate (See Figure 9 and Table 8). Eighty percent of the hazard scores were assigned by prediction software and authoritative sources.

Acute Aquatic Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	2					2
vL						
L		1	19	12	10	42
M		1	8	8	1	18
H		2	6	7	2	17
vH		4	9	11	1	25
Total	2	8	42	38	14	90

Table 7 Acute Aquatic Toxicity Data

The hazard score for acute aquatic toxicity relied primarily on classifications and lists by authoritative sources, such as the Canadian Domestic Substances List (DSL) and various GHS or European Commission categorizations. When the chemical was not listed or classified as toxic to aquatic organisms by an authoritative source, the score was based on empirical LC_{50}, EC_{50}, or range of K_{ow} or water solubility values when identified. As a result, the overall score for acute aquatic toxicity may have been based on single species/study. If data for more than one species/study were identified, the most conservative value served as the basis of the hazard score. When empirical data were not identified, U.S. EPA (2011) ECOSAR, Vega QSAR Models, and U.S. EPA T.E.S.T software were used to predict acute aquatic toxicity values based on the assigned chemical class (US Environmental Protection Agency, 2018c, 2018b; Vegahub.eu, 2017).

The majority of very-High hazard scores were given by authoritative sources and modeling software.

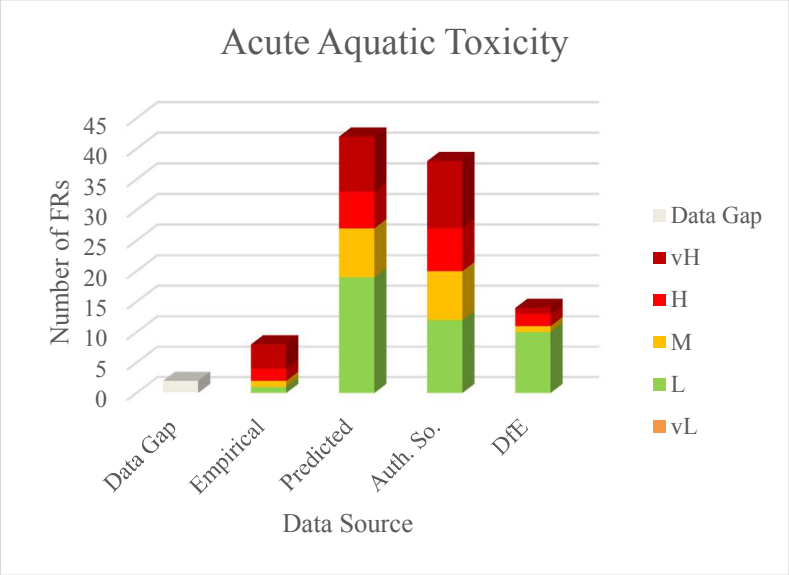


Figure 9 Acute Aquatic Toxicity Data

Persistence

The Persistence hazard score was overwhelmingly very-High for the OHRF class with 85 compounds out of 90 receiving the very-High hazard score (See Figure 10 and Table 9). The majority of scores were assigned based on authoritative sources.

Persistence	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	1					1
vL						
L						
M						
H				4	1	4
vH		7	28	50	10	85
Total	1	7	28	54	11	90

Table 8 Persistence Data

The hazard score for persistence relied primarily on Persistent Organic Pollutants (POP) or Persistent Bioaccumulative and Toxic Substance (PBT) classifications and lists by authoritative sources. Of the OHFR that were not listed or classified as a POP or PBT, the hazard score for persistence was based on EPI-Suite™ model estimates for half-lives in soil, water, and sediment, since most screened OHFR did not have empirical data for these parameters (US Environmental Protection Agency, 2012). Again, the hazard score was based on the most conservative value (soil, sediment, or air). Vega QSAR prediction software was also occasionally used to determine the persistence in soil, sediment, and water. The Persistence endpoint had the highest number of very-High scores of any endpoint. This is consistent with the known high stability and electronegativity of the halogen compounds.

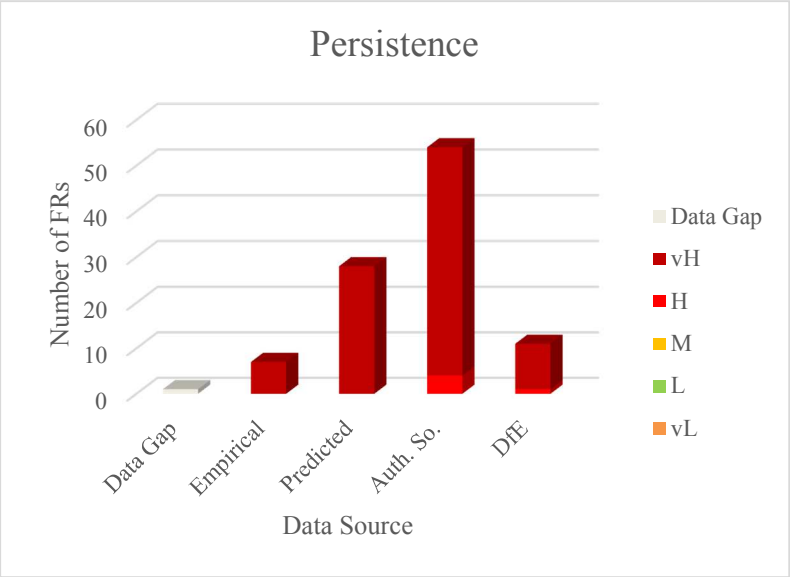


Figure 10 Persistence Data

Bioaccumulation

The typical hazard score for this endpoint was very-High as 44 of the 90 compounds received the highest hazard score for bioaccumulation (See Figure 11 and Table 10). Twenty-seven of the compounds received a High grade and the majority of the very-High and High grade designations came from authoritative sources and relied primarily on POP or PBT classifications and lists.

Bioaccumulation	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	1					1
vL		1	4	2		7
L			5	3	3	8
M			2	1		3
H			11	16	6	27
vH		4	6	34	3	44
Total	1	5	28	56	12	90

Table 9 Bioaccumulation Data

For many of the other compounds, the hazard score was based on K_{ow} and bioaccumulation or bioconcentration factors (BAF/BCF), which were generally predicted using U.S. EPA EPI-Suite and U.S. EPA T.E.S.T. software since empirical data were not identified (US Environmental Protection Agency, 2012, 2018c). Using this prediction software, 4 OHFR received a hazard designation of very-Low. Of these 4, one (CAS # 90075-91-5) received a Benchmark Grade of F while the others received C grades. The majority of the scores given by the prediction software for this endpoint were High.

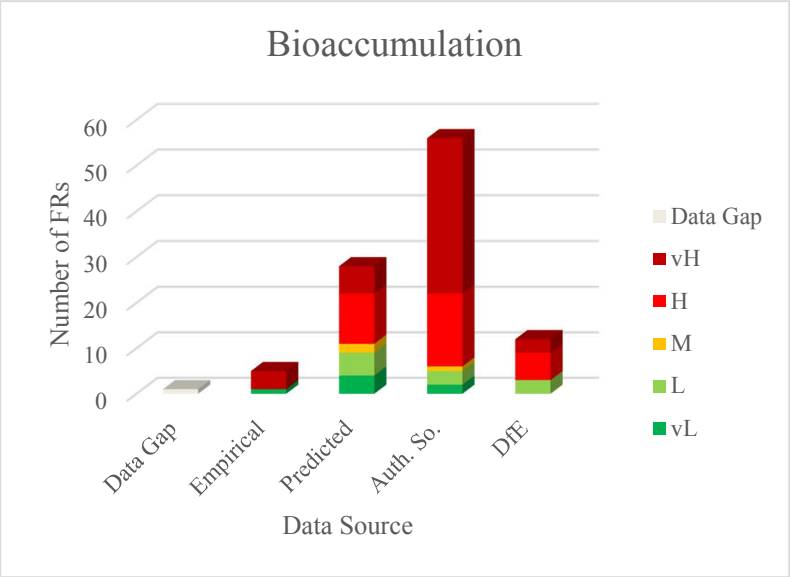


Figure 11 Bioaccumulation Data

Overall Assessment

The following section will be an overall analysis of the nine endpoints associated with the QCAT© methodology. Appendix 2 has a holistic depiction of the data gathered listed by the associated endpoint.

In this study, the Initial and Benchmark (Final) Grades were identical, which from our experience and that of others (Department of Ecology, 2018), this is not typical (Table 11). No OHFR achieved a Benchmark Score of A and only two compounds (88497-56-7 (polymer) and 135229-48-0 (polymer)) received a score of B. Both of these polymers also received a B score from the US EPA's DfE program. A group of 16 flame retardants received a Benchmark score of C, while the remaining 72 flame retardants failed. Of these 72 failed flame retardants, 2 received an F_{DG} grade meaning there was not enough information available for an initial or final Benchmark Grade to be assigned.

Initial and Final Grade	*Number of FRs*
A	0
B	2
C	16
F	72

Table 10 OHFR Final Grade

Most of the screened OHFR received an F indicating high hazard by empirical data, QSAR model predictions, and/or excessive data gaps. Acute Toxicity was the most prominent potential health hazard identified based on empirical data (See Appendix 2). Endpoints with the most prevalent data gaps were Reproduction Toxicity (20) and Endocrine Disruption (18), due to the lack of identified empirical data or computer models able to predict this hazard (See Appendix 2). The vast majority of all very-High ratings were given to the environmental toxicity concerns and not the human health

endpoints (See Appendix 2). While only 7 compounds received a score of very-Low, all were from the predicted endpoint for bioaccumulation (See Appendix 2).

Discussion

In this hazard screen, we used the Quick Chemical Assessment Tool (QCAT©) method (Stone, 2016) to screen 90 OHFR. The 9 human and environmental health categories included in the QCAT© originated from and encompass half of 18 hazard categories included in the more comprehensive and data-intensive GreenScreen® and U.S. EPA DfE approaches. Complete GreenScreen® reports are rarely accomplished due to the lack of information and overabundance of data gaps (Brown, 2012). Given the limited amount of information available on the OHFR, we decided to perform the QCAT© approach instead of the GreenScreen® methodology. The publishers of QCAT©, Washington State's Department of Ecology, advertise this methodology for "…small and medium businesses use…" although as proven it can easily be adapted for use for assessment of classes of chemicals (Stone, 2016). To date, only 20 compounds have been assessed and published on the Department of Ecology's associated website using the QCAT© method (Department of Ecology, 2018). Using this adapted methodology a representative sample of 90 halogenated flame retardants was chosen. Only two of the evaluated flame retardants received a passing grade of B and none received an A. Of the 90 flame retardants assessed, 72 received a Benchmark grade of F. By looking at the class as a whole, some prominent generalizations can be made. As a class, the OHFR are typically classified as:

- Very Persistent
- Bioaccumulative
- Lacking information for Reproductive Toxicity
- Lacking information for Endocrine Disruption

In addition, simple non-branched structures are generally non-toxic while still persistent and OHFR having less than 3 halogens correlates to less toxicity.

Environmental Quality Endpoints

The highest concentration of very-High and High hazard scores were found among the three Environmental Quality Endpoints (Acute Aquatic Toxicity, Persistence, and Bioaccumulation). The most notable being Persistence which had 84 hazard scores of very-High for the 90 compounds assessed. Strong bonding due to high electronegativity is a hallmark of halogenated compounds which leads to their long persistence in the environment and the human body (Zhang et al., 2016). An example of this persistence is Tetrabromobisphenol A diglycidyl ether (CAS 3072-84-2) which has a reported half-life of 180 days in water, 360 days in soil, and 1620 days in sediment. This longevity is not restricted to the flame retardants that received a failing grade as this compound received an overall grade of C even with this notable persistence.

The tendency towards very-High and High hazard scores was also seen for Bioaccumulation where 44 compounds received a grade of very-high and 27 High. Interestingly, this endpoint also had 7 hazard scores of very-Low and 8 of Low. Almost all of the very-Low hazard scores were based on QSAR predictions with the exception of

Chlorendic Acid (CAS 115-28-6) which was based on toxicological studies. The compounds given the favorable scores had simple structures with little branching. However, the compounds that received a favorable final Benchmark (C or B) score still largely received a very-High hazard score for persistence.

Endocrine Disruption

As a group of OHFR, the Endocrine Disruption endpoint had 18 Data Gaps. This endpoint did include 57 hazard scores based on authoritative sources with the 53 being assigned a High hazard score. The largest problem with the evaluation of this endpoint is a lack of standardization as to what constitutes Endocrine Disruption (Evans, 2012; Hodgson, 2010). This can be further seen in the high reliance of the QCAT© methodology on authoritative sources in this area. Within the QCAT© guidance, there are no specific guidelines for a hazard score based on empirical evidence for endocrine disruption. It should be noted that the United States government has numerous lists and databases that contain possible endocrine disruptors based primarily on modeling and "Read-Across" methods (Center for Disease Control, 2018; US Environmental Protection Agency, 2018a). However, the basis for these lists varies and has not been standardized. This represents an important area where consensus needs to be reached.

Chemical Class Assessments

Hazard screening methods such as QCAT© and GreenScreen® are valuable tools for collecting public information on potential hazards and for identifying critical data gaps

which can stimulate additional and targeted research. Specifically, QCAT© has the advantage of being time efficient and effective as an initial source of information before additional time and effort are spent on a full GreenScreen® evaluation. This approach can also be useful to inform the initial stages of policy-making decisions on the potential human health and environmental impacts of chemicals in the environment. It also provides a systematic way to assess basic health and environmental risks of compounds without requiring in-depth scientific knowledge. However, a baseline understanding of chemical processes and scientific software is necessary, and general training is required to correctly use the various modeling software programs and interpret results.

Limitations of these screening methods, particularly in the case of OHFR, are that the chemical space occupied by some complex chemical structures and mixtures may fall outside the models' applicability domains. In addition, the SMILES notations often relied upon in some QSAR models, are not unique chemical fingerprints. When CAS registry numbers have not been assigned to compounds, the assessment is largely left to SMILE notations which may not be specific for the compound of interest. In addition, many prediction software packages such as Vega QSAR are entirely dependent on these SMILE notations while others have different requirements such as Epi-Suite which requires both a CAS registry number and a SMILE notation.

The OHFR present a challenge when cross-checking hazard lists since some of these lists are based on suspected hazard attributes, and not necessarily empirical data. For example, Pharos, which is recommended in the QCAT© methodology, considers any member of the brominated group to have a concern for Endocrine Disruption (Stone, 2016).

Whereas, a chemical listing in the TEDX database of suspected Endocrine Disruptors requires a positive result in at least one empirical study. Also, many lists such as the ECHA C&L Registry have the support of empirical evidence although it can be a challenge to find this information. In addition, through various portals such as U.S. EPAs ChemView, information is accessible but the empirical evidence on which the information is based may only be found within other reports or websites.

We recommend that a hierarchy be established for a complete screening-level assessment of classes of chemicals. This systematic approach, as seen in Appendix 3, utilizes established methods and processes to allow a quick assessment of classes of chemicals to identify a smaller number that would be considered for more widespread use such as in common consumer goods. In our recommended approach, groups of chemicals first undergo screening using the QCAT© methodology where existing information is acquired from public sources to determine their toxicity and properties. Only the compounds that pass the QCAT© assessment will then proceed to a GreenScreen® assessment. After the GreenScreen® assessment, key remaining data gaps would be prioritized for completion, most likely from empirical data from commissioned studies. In this way, critically needed information would be identified and relatively few studies will need to be completed.

From this study, it is clear that there are a substantial number of unknowns with regards to the adverse health and environmental effects of halogenated flame retardants. For most of these unknowns, there is prediction software that has been developed that covers the applicable chemical domains to successfully allow the estimation of endpoints

which otherwise would be data gaps. However, it would seem wise to conduct some additional experimental studies to verify at least some of the predictions made by the various software. Endpoints, where the need appears to be high, include Carcinogenicity, Mutagenicity/Genetic Toxicity, Developmental Toxicity, and Acute Aquatic Toxicity which all heavily relied upon prediction software. In particular, more research should be conducted on the Endocrine Disruption and Reproductive Toxicity endpoints which had the highest percentage of data gaps. As eighty percent of the OHFR screened received failing grades, these results show that a large number of flame retardants currently in use or being considered for use potentially have serious toxicological or environmental side effects. This, combined with the knowledge that these assessments data relied heavily on predictions, is also a cause for further research and evaluation.

Limitations of the QCAT© Approach

The QCAT© method is an adequate initial hazard assessment. Since it does not include the full range of endpoints, requires less burden of proof, and heavily relies upon pre-determined authoritative sources, it is not as comprehensive as more extensive approaches such as GreenScreen®. QCAT© is a hazard assessment meaning it measures the potential for a compound to induce harm. It does not link this potential to exposure levels and does not evaluate risk. For example, a chemical can exhibit substantial toxicity but if there is little to no exposure then there is a low risk. A compound given any Benchmark grade should be evaluated for potential for exposure before a regulatory decision should be made.

As indicated above, the QCAT© assessment depends on authoritative sources and does not involve a complete or independent evaluation of the scientific literature. As a result, there may be data which was not assessed by these authoritative sources that could affect the final Benchmark grade. As with any assessment, new studies may have been performed or published after the agency evaluation which have not been captured in our QCAT© screen. However, we are not aware of major deficiencies in the evaluations of the authoritative groups that were used for this study and believe that the information assessed is a fair representation of publicly available information on these compounds.

Conclusion

To our knowledge, this is the first large systematic assessment that has used QCAT© as an assessment tool. It has allowed a relatively quick distillation of the potential toxicity of 90 halogenated flame retardants and has identified the most promising non-toxic compounds, which resulted in 2 compounds that received a grade of B. We recommend that these compounds undergo a GreenScreen® assessment for a more comprehensive evaluation if widespread use and consumer exposure is anticipated. As indicated above, in 2017, the US Consumer Products Safety Commission began to initiate rulemaking in order to phase out halogenated flame retardants from certain consumer products and ultimately phase out of them altogether (Consumer Product Safety Commission, 2017). This was the result of decades of research and deliberations which may have been greatly shortened if a systematic approach to assess toxicity, such as the one described in this article, had been undertaken. With the phasing out of the halogenated flame retardants, organophosphate flame retardants have been increasingly used in consumer products as replacements. Further study in a systematic approach needs to be undertaken to fully understand the toxicity of both classes to further protect human and environmental health.

References - Chapter 1

Anastas, P. T., Heine, L., & Whittaker, M. H. (2018). How Chemical Hazard Assessment in Consumer Products Drives Green Chemistry. In *Handbook of Green Chemistry*. https://doi.org/10.1002/9783527628698.hgc131

Aschberger, K., Campia, I., Pesudo, L. Q., Radovnikovic, A., & Reina, V. (2017). Chemical alternatives assessment of different flame retardants – A case study including multi-walled carbon nanotubes as synergist. *Environment International*, *101*, 27–45. https://doi.org/10.1016/j.envint.2016.12.017

Blum, A., Daley, R., & Babrauskas, V. (2011). Regulatory policy leading to halogenated flame retardants in furniture and baby products: fire safety and health concerns. *Organohalogen Compounds*, *73*, 2032–2035.

Brown, V. J. (2012). Why is it So Difficult to Choose Safer Alternatives for Hazardous Chemicals? *Environmental Health Perspectives*, *120*(7), A281–A283. https://doi.org/10.1289/ehp.120-a280

Canadian Substances Registry (DSL). (2018). Retrieved from https://pollution-waste.canada.ca/substances-search/Substance?lang=en

Center for Disease Control. (2018). *RTECS*. Retrieved from http://ccinfoweb.ccohs.ca/rtecs/search.html

Cequier, E., Ionas, A. C., Covaci, A., Marc??, R. M., Becher, G., & Thomsen, C. (2014). Occurrence of a broad range of legacy and emerging flame retardants in indoor environments in Norway. *Environmental Science and Technology*, *48*(12), 6827–6835. https://doi.org/10.1021/es500516u

Commission, U. C. P. S. (2013). *CPSC - Bans TRIS-Treated Children ' s Garments*.

Consumer Product Safety Commission. (2017). Guidance Document on Hazardous Additive, Non-Polymeric Organohalogen Flame Retardants in Certain Consumer Products.

Cooper, E. M., Kroeger, G., Davis, K., Clark, C. R., Ferguson, P. L., & Stapleton, H. M. (2016). Results from Screening Polyurethane Foam Based Consumer Products for Flame Retardant Chemicals: Assessing Impacts on the Change in the Furniture Flammability Standards. *Environmental Science and Technology*, *50*(19), 10653–10660. https://doi.org/10.1021/acs.est.6b01602

Cordner, A., Mulcahy, M., & Brown, P. (2013). Chemical regulation on fire: Rapid policy advances on flame retardants. *Environmental Science and Technology*,

47(13), 7067–7076. https://doi.org/10.1021/es3036237

de Boer, J., Ballesteros-Gómez, A., Leslie, H. A., Brandsma, S. H., & Leonards, P. E. G. (2016). Flame retardants: Dust - And not food - Might be the risk. *Chemosphere*, *150*, 461–464. https://doi.org/10.1016/j.chemosphere.2015.12.124

Department of Consumer Affairs Technical Bulletin 117-2013. (2013), (June).

Department of Ecology. (2018). Chemical Hazard Assessment Database. Retrieved February 9, 2019, from http://theic2.org/hazard-assessment

Deutsche, & Forschungsgemeinschaft. (2018). *List of MAK and BAT Values*. Retrieved from https://onlinelibrary.wiley.com/doi/pdf/10.1002/9783527812127

European Chemicals Agency. (2015). Understanding Reach.

Evans, T. J. (2012). *Reproductive Toxicity and Endocrine Disruption*. *Veterinary Toxicology* (Third Edit). Elsevier Inc. https://doi.org/10.1016/B978-0-12-811410-0.00017-9

Gold, M. D., Blum, A., & Ames, B. N. (1978). Another flame retardant, tris-(1,3-dichloro-2-propyl)-phosphate, and its expected metabolites are mutagens. *Science*, *200*(4343), 785–787. https://doi.org/10.1126/science.347576

Hodgson, E. (2010). *A Textbook of Modern Toxicology* (4th ed.). Hoboken, New Jersey: John Wiley & Sons, Inc.

IARC. (2010). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. VOLUME 99 Some aromatic amines, organic dyes, and related exposures. IARC*. https://doi.org/10.1016/S1470-2045(08)70089-5

Larsson, K., De Wit, C. A., Sellström, U., Sahlström, L., Lindh, C. H., & Berglund, M. (2018). Brominated Flame Retardants and Organophosphate Esters in Preschool Dust and Children's Hand Wipes. *Environmental Science and Technology*, *52*(8), 4878–4888. https://doi.org/10.1021/acs.est.8b00184_arxiv

Lavoie, E. T., Heine, L. G., Holder, H., Rossi, M. S., Lee, R. E., Connor, E. A., … Davies, C. L. (2010). Chemical alternatives assessment: Enabling substitution to safer chemicals. *Environmental Science and Technology*, *44*(24), 9244–9249. https://doi.org/10.1021/es1015789

Lignell, S., Aune, M., Darnerud, P. O., Stridsberg, M., Hanberg, A., Larsson, S. C., & Glynn, A. (2016). Maternal body burdens of PCDD/Fs and PBDEs are associated with maternal serum levels of thyroid hormones in early pregnancy: A cross-sectional study. *Environmental Health: A Global Access Science Source*, *15*(1). https://doi.org/10.1186/s12940-016-0139-7

National Toxicology Program. (2016). *14th Report on Carcinogens*. Retrieved from https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html

NCBI. (2018). PubMed. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

October, G., & October, S. (2015). Assembly Bill No. 127, (127), 1–2.

OECD.org. (2018). OECD QSAR Toolbox. Organization for Economic Co-operation and Development. Retrieved from http://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

OEHHA. (2018). *Proposition 65*. Retrieved from https://oehha.ca.gov/proposition-65/proposition-65-list

Safer Chemicals Database. (2018). Chemical Hazard and Alternatives Toolbox-ChemHat). Retrieved from http://www.chemhat.org/en/about-chemhat/who-made-chemhat

Stapleton, H. M., Klosterhaus, S., Eagle, S., Fuh, J., Meeker, J. D., Blum, A., & Webster, T. F. (2009). Detection of organophosphate flame retardants in furniture foam and U.S. house dust. *Environmental Science and Technology*, *43*(19), 7490–7495. https://doi.org/10.1021/es9014019

Stapleton, H. M., Klosterhaus, S., Keller, A., Ferguson, P. L., Van Bergen, S., Cooper, E., … Blum, A. (2011). Identification of flame retardants in polyurethane foam collected from baby products. *Environmental Science and Technology*, *45*(12), 5323–5331. https://doi.org/10.1021/es2007462

Stone, A. (2016). *Quick Chemical Assessment Tool Version 2.0*. Olympia, Washington: Department of Ecology-Washington State.

Ted.com. (2018). TEDX. The Endocrine Disruption Exchange. Retrieved from https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list

The European Parliament and the Council of the European Union. (2003). *Directive 2003/11/ EEC of the European Parliament* (Vol. 16).

U.S. National Library of Medicine. (2018). ChemIDplus. Bethesda: ToxNet. Retrieved from https://chem.nlm.nih.gov/chemidplus/

Union, E. (2018). *ECHA*. Retrieved from https://echa.europa.eu/information-on-chemicals/registered-substances

US Environmental Protection Agency. (2012). EPI Suite^{TM}-Estimation Program Interface. Environmental Protection Agency. Retrieved from https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

US Environmental Protection Agency. (2018a). Collaborative Estrogen Receptor Activity Prediction Project. Retrieved from https://comptox.epa.gov/dashboard/chemical_lists/CERAPP

US Environmental Protection Agency. (2018b). Ecological Structure Activity Relationships (ECOSAR) Predictive Model. US Environmental Protection Agency. Retrieved from https://www.epa.gov/tsca-screening-tools/ecological-structure-activity-relationships-ecosar-predictive-model

US Environmental Protection Agency. (2018c). Toxicity Estimation Software Tool (TEST). US Environmental Protection Agency. Retrieved from https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test

US Environmental Protection Agency. (2018d). US ChemView. Retrieved from https://chemview.epa.gov/chemview

US EPA, O. of P. P. (2014). About Pesticides | Pesticides | US EPA. *05/08/2014*.

van I, der V., & de, B. J. (2012). Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. *Chemosphere*, *88*(1879–1298 (Electronic)), 1119–1153.

Vegahub.eu. (2017). VEGA. Retrieved from https://www.vegahub.eu/

Wu, W., & Yang, C. Q. (2006). Comparison of different reactive organophosphorus flame retardant agents for cotton: Part I. The bonding of the flame retardant agents to cotton. *Polymer Degradation and Stability*, *91*(11), 2541–2548. https://doi.org/10.1016/j.polymdegradstab.2006.05.010

Xu, F., Giovanoulis, G., Van Waes, S., Padilla-Sanchez, J. A., Papadopoulou, E., Magnér, J., … Covaci, A. (2016). Comprehensive study of human external exposure to organophosphate flame retardants via air, dust, and hand wipes: The importance of sampling and assessment strategy. *Environmental Science and Technology*, *50*(14), 7752–7760. https://doi.org/10.1021/acs.est.6b00246

Zhang, X., Sühring, R., Serodio, D., Bonnell, M., Sundin, N., & Diamond, M. L. (2016). Chemosphere Novel flame retardants : Estimating the physical – chemical properties and environmental fate of 94 halogenated and organophosphate PBDE replacements. *Chemosphere*, *144*, 2401–2407. https://doi.org/10.1016/j.chemosphere.2015.11.017

Zota, A. R., Park, J. S., Wang, Y., Petreas, M., Zoeller, R. T., & Woodruff, T. J. (2011).

Polybrominated diphenyl ethers, hydroxylated polybrominated diphenyl ethers, and measures of thyroid function in second trimester pregnant women in California. *Environmental Science and Technology*, *45*(18), 7896–7905. https://doi.org/10.1021/es200422b

Appendixes

Appendixes will be located at the end of this thesis separated by Chapter for ease of use and fluency.

Chapter 2

A Screening-Level Hazard Assessment of Human and Environmental Health Endpoints of Organophosphate Flame Retardants

Introduction

Flame retardants are a wide class of compounds used to inhibit, reduce, and stop the spread or ignition of flames. Traditionally, halogenated flame retardants were used to meet elective or mandated safety requirements. In recent years, many human and environmental health concerns have caused researchers and industry leaders to look for safer less toxic alternatives to the halogenated flame retardants. In 2017, the US Consumer Products Safety Commission granted Petition HP 15-4 which will allow the regulation of halogenated flame retardants, as a class, in certain consumer products (Blum, Daley, & Babrauskas, 2011; Consumer Product Safety Commission, 2017; Stapleton et al., 2011). Similarly, in 2018 the California legislature passed a bill which now prohibits the manufacturing and sale of select consumer products containing toxic flame retardants, including halogenated flame retardants, within the state (Bloom & Kalra, 2018). These events have led to the use of alternative types of flame retardants, most notably organophosphate flame retardants (OPHR). Organophosphates are efficient flame retardants since they can inhibit combustion by releasing phosphoric acid when exposed to heat which interferes with the combustion process by favoring char formation due to incomplete combustion (Aschberger, Campia, Pesudo, Radovnikovic, & Reina, 2017). This class of compounds includes organic phosphates, phosphonates, and phosphinates, which are already often used in plastics, textiles, polyurethane foams, coatings and rubber, and in electronics. Since they are primarily used in consumer products, they are not heavily regulated and little toxicological information is known for

many of them.

Due to safety concerns and the fact that they will replace halogenated flame retardants, we decided to investigate OPFR as a group to assess what toxicological information is currently known and what needs to be investigated further. OPFR research has dated back to the 1970s when Dr. B. Ames and a student working in his lab, now Dr. A. Blum, conducted research into the mutagenicity and potential carcinogenicity of Tris(2,3-dibromopropyl) phosphate, a flame retardant to which children were exposed through their pajamas (Blum & Ames, 1977). Following this initial study and the ensuing ban on Tris(2,3-dibromopropyl) phosphate in children's clothing, several Tris-related compounds have been developed and are currently in the market. These types of product replacement do not necessarily reflect toxicity but do show how even though one compound is phased out, those serving as replacements may be very similar and may exhibit the same or similar health consequences, and not be regulated. For example, this study included 8 Tris-related compounds similar to the previously banned Tris(2,3-dibromopropyl) phosphate among the 97 total organophosphate flame retardants that were investigated (See table 12).

Chemical Name	*CAS #*
Tris(2,3-dibromopropyl) phosphate	126-72-7
Tris(2-butoxyethyl) phosphate	78-51-3
Tris(2-chloroethyl) phosphate	115-96-8
Tris(2-chloroethyl) phosphite	140-08-9
Tris(2-chloroisopropyl) phosphate	13674-84-5
Tris(2-chloropropyl) phosphate	6145-73-9
Tris(2-ethylhexyl) phosphate	78-42-2
Tris(1,3-dichloro-2-propyl)phosphate	13674-87-8

Table 11 Tris-Family

Given this pattern of replacement, it is critical that a systematic assessment be conducted to quickly and efficiently determine key aspects of the toxicity of chemical compounds currently in usage. As indicated in the previous chapter, our research group used the Quick Chemical Assessment Test (QCAT©) developed by Washington State's Department of Ecology as a first pass screening assessment (Stone, 2016). The current study applies the existing QCAT© method with subsequent consideration of GreenScreen® endpoints for a more systematic approach in assessing an entire class of chemicals. The primary objective of this study was to conduct a screening-level assessment of a broad range of health and environmental hazard endpoints for an expansive range of OPFR, and present the resulting information so that the effects and evaluations of the chemicals in this class can be easily compared using a systematic approach.

Materials and Methods

Hazard Screening Methodology

As described in Chapter 1, a slightly modified Quick Chemical Assessment Tool (QCAT©) methodology was used to evaluate the hazards of the OPFR. In addition, GreenScreen® information was also used as a subsequent tool when it was available (Stone, 2016). In accordance with the QCAT© methodology, a full literature review was not conducted thecompound being assessed. The primary modification was that when both empirical and predicted data were available, empirical data was given priority when assigning a hazard score and grade.

Flame Retardant List

The list of organophosphate flame retardants to be evaluated was compiled from existing lists obtained from the U.S. EPA, lists of flame retardants with high commercial usage, from the Tox21 database, flame retardant experts, and previously published studies (Blum, 2018; Paules, 2018; van I & de, 2012; Wei et al., 2015; Windham et al., 2015). A total of 97 OPFR were selected for assessment and reflect flame retardants already in use, or those for which increased usage is anticipated. The complete list including CAS registry numbers and names can be found in Appendix 2.

Public Database Searches for Toxicity Data

To evaluate the various chemicals, their specific Chemical Abstract Services (CAS) registry numbers were used as the primary identifiers. In addition to the CAS

numbers, the corresponding Simplified Molecular Input Entry System (SMILE) notations were used as identifiers for QSAR purposes. These were found using ChemIDplus, PubMed, or the PubChem Sketcher tool (NCBI, 2018; U.S. National Library of Medicine, 2018).

Authoritative databases were used to access existing hazard screens or toxicity reviews. The selected databases are open access although some of the specific supporting data are not publicly available. Examples of the primary databases and existing hazard screens used in this evaluation include:

- U.S. EPA Design for the Environment program (DfE)(US Environmental Protection Agency, 2018d),
- European Chemicals Agency database (EUROPEAN UNION, 2018),
- TEDX (Ted.com, 2018),
- Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency/Prop 65 lists (OEHHA, 2018),
- International Agency for Research on Cancer,
- Deutsch Mak list (Deutsche & Forschungsgemeinschaft, 2018),
- OSPAR rating (Safer Chemicals Database, 2018),
- San Antonio Statement on Brominated and Chlorinated Flame Retardants,
- Health Canada/Canadian Environmental Protection Agency(*Canadian Substances Registry (DSL)*, 2018).

Other more expansive databases used include ChemHat, ChemView, ChemIDplus, and PubMed (NCBI, 2018; Safer Chemicals Database, 2018; U.S. National

Library of Medicine, 2018; US Environmental Protection Agency, 2018d). In five cases where a Design for Environment (DfE) report had already been conducted on the compound, DfE information was used in place of Step 1 and Step 2 sources. DfE evaluation covers all endpoints associated with QCAT© except Endocrine Disruption which was often a Data Gap for all evaluations that we conducted (US EPA, 2018d). The QCAT© methodology provides specific websites and databases for use for specific endpoints, although being several years old some of the URLs no longer worked or were corrupted. For a full list of databases and URLs used, and QCAT© flow chart, please see Appendix 1 and 3.

Initial Grade

In order to assign the initial hazard score for each endpoint, data from open access sources, modeling software, databases, and studies were collected. The available data were then compiled into a hazard score ranging from very-Low to very-High using the established QCAT© criteria for the endpoint in question. The QCAT© methodology separates types and sources of data into two groups, Step 1 authoritative sources and Step 2 less-authoritative sources (See Figure 12). If a Step 1 authoritative source was available, such as the FR's listing on the German MAK list for the Developmental Toxicity or an IARC list, then there was no need for additional data gathering, or to

	Human Health: Developmental (including Developmental Neurotoxicity)		
	High (H)	Moderate (M)	Low (L)
Step I Sources			
#	Priority Sources		
10	**EU - R-phrases** R61 - May cause harm to the unborn child R64 - May cause harm to breastfed babies	**EU - R-phrases** R63 - Possible risk of harm to the unborn child	
11	**MAK** Pregnancy Risk Group A Pregnancy Risk Group B	**MAK** Pregnancy Risk Group C Pregnancy Risk Group D	
18	**US NIH - Reproductive & Developmental Monographs** Clear Evidence of Adverse Effects - Developmental Toxicity Some Evidence of Adverse Effects - Developmental Toxicity Limited Evidence of Adverse Effects- Developmental Toxicity	**US NIH - Reproductive & Developmental Monographs** Some Evidence of no Adverse Effects - Developmental Toxicity Limited Evidence of no Adverse Effects - Developmental Toxicity Insufficient Evidence for a Conclusion - Developmental Toxicity	**US NIH - Reproductive & Developmental Monographs** Clear Evidence of no Adverse Effects - Developmental Toxicity
#	Secondary Sources		
12	**Japan - GHS** Category 1, 1A or 1B: Known/Presumed to induce developmental toxicity	**Japan - GHS** Category 2: Suspected to induce developmental toxicity	**Japan – GHS** Not classified (sufficient information; chemical is not problematic)
13	**Korea - GHS** Category 1, 1A or 1B: Known/Presumed to induce developmental toxicity	**Korea – GHS** Category 2: Suspected to induce developmental toxicity H362: May cause harm to breast-fed children	
14	**New Zealand - GHS** 6.8A or 6.8C - Indication of developmental toxicity	**New Zealand - GHS** 6.8B - Indication of developmental toxicity	
19	**Boyes – Neurotoxicants** Developmental Neurotoxicity		
20	**G&L - Neurotoxic Chemicals** Developmental Neurotoxicant Developmental Neurotoxicant (2014)		
Step II Sources			
16	**ECHA C&L Inventory** Use classification (e.g., Category 1) or H-Statement as shown in Step I above	**ECHA C&L Inventory** Use classification (e.g., Category 1) or H-Statement as shown in Step I above	
17	**EU RA, IUCLID Datasheet, RTECS, HSDB, UNEP SIDS, OSHA, Danish Q(SAR), etc.** Strong evidence of developmental toxicity	**EU RA, IUCLID Datasheet, RTECS, HSDB, UNEP SIDS, OSHA, Danish Q(SAR), etc.** Indication of developmental toxicity	**EU RA, IUCLID Datasheet, RTECS, HSDB, UNEP SIDS, OSHA, Danish Q(SAR), etc.** Indication of no developmental toxicity

Figure 12 Grading Rubric (Stone, 2016)

continue to Step 2 sources. If Step 1 sources were unavailable then Step 2 sources where investigated. For an endpoint to receive a hazard grade, there had to be a single Step 1 source or two complimentary Step 2 Sources. If only one Step 2 source, deemed reliable by the accessor, could be found, a hazard score can be assigned according to the QCAT© methodology with the specific notation (Stone, 2016). In another minor modification to the QCAT© method used for our studies, if QSAR data were to be used, two complimentary QSAR data sources were required to determine a hazard score. In the QCAT© guidance document, the use of QSAR data was not explicitly detailed for each endpoint, so for this assessment, it was treated as a Step 2 source. As indicated above, in situations where empirical data and prediction data differed substantially, empirical data was used to set the hazard grade. In most cases, empirical data were generally consistent with the prediction software results and supported the designation given by a Step 1

source. In situations where a grade could not be assessed due to the lack of data from any of the specified sources, a "DGap or Data Gap" notation was given. Once all endpoints had been assessed, their scores were compared to produce an Initial Grade using criteria described in the QCAT© guidance document (Stone, 2016). The Initial Grade is assigned without consideration of Data Gaps that may exist.

Significance Testing

To determine if there is any significant difference in toxicity between the organophosphate flame retardants and the halogenated flame retardants, assessed in Chapter 1 the Wilcox test was used through RStudio Statistical software (Rstudio Team, 2016; Team & R Development Core Team, 2016). The Wilcox test is a nonparametric equivalent of a paired samples t-test since the data was largely nonparametric a standard t-test was deemed to be unfit to access the significance (Wilcoxon, 1950). The results from the Wilcox test were so non-significant a Bonferroni's multiple comparisons p-value adjustment was not needed, although it was done. (Tamhane & Gou, 2017)(See Appendix 5). Significance was based on traditional α=0.05.

Results

The following section reports details of the results found for each endpoint investigated. Figure 13 shows a heat map of the compounds with robust datasets that were evaluated and the initial and final scores assigned. Seventeen compounds that received a grade of F_{DG} for having an excess amount of data gaps are not shown due to space limitations (see Fig. XXX in Appendix). Within the heat map, each color corresponds with a hazard score: very-Low is shown as dark green, Low as light green, Moderate as yellow, High as red, and very-High as dark red. General patterns that can be seen by looking at the heat map include Moderate hazard scores typically seen for Developmental Toxicity, High to very-High Hazard scores for Acute Aquatic Toxicity and Persistence, and very-Low to Low scores for Bioaccumulation. Four compounds (115-86-6, 35948-25-5, 77226-90-5, 68664-06-2) had previously been assessed using the DfE approach, each of which retained their DfE hazard scores in this assessment. To see the full QCAT© data, see Appendix 6. The results for each of endpoints is discussed in more detail below.

Organophosphate Flame Retardants
Heat Map

CAS #	Initial	Final	AT	C	R	D	M	E	AA	P	B
126-72-7	F	F	H	H	H	M	H	H	vH	vH	vH
78-51-3	F	F	M	M	M	M	M	H	L	vH	vL
115-96-8	F	F	M	H	H	H	vH	H	H	vH	vH
140-08-9	F	F	vH	H	dg	L	M	M	M	M	L
13674-84-5	F	F	H	H	H	H	M	H	M	vH	H
6145-73-9	F	F	M	H	M	M	L	L	vH	vH	vL
78-42-2	F	F	vH	H	L	L	L	H	vH	M	L
1241-94-7	F	F	H	dg	M	M	H	H	vH	H	H
756-79-6	F	F	M	M	M	M	H	L	H	M	vL
13674-87-8	F	F	H	H	M	M	M	H	H	vH	H
1330-78-5	F	F	M	M	M	M	M	H	vH	vH	H
115-86-6	F	F	L	M	L	L	L	H	vH	M	M
512-56-1	F	F	M	H	M	M	H	L	L	vH	vL
56803-37-3	F	F	M	L	M	M	L	M	vH	vH	vH
68937-41-7	F	F	L	L	M	M	L	M	H	vH	vH
126-73-8	F	F	H	H	L	M	L	H	H	vH	L
563-04-2	F	F	vH	L	M	M	L	M	vH	H	L
78-30-8	C	C	vH	L	M	M	M	M	M	M	H
15091-98-2	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
68915-31-1	B	F	L	dg	dg	dg	dg	dg	dg	vH	dg
2524.04.1	C	F	vH	dg	L	L	L	dg	H	M	vL
29761-21-5	F	F	L	M	M	M	M	L	vH	vH	vH
20445-94-7	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
838-85-7	C	C	M	L	dg	M	L	dg	vH	M	vL
813-78-5	C	C	M	M	M	M	M	M	M	vH	vL
26444-49-5	C	C	M	L	M	M	L	L	H	L	M
52628-03-2	B	F	M	dg	dg	M	dg	dg	dg	dg	dg
868-85-9	B	B	H	M	M	M	M	L	M	M	vL
78-38-6	C	C	M	M	dg	M	L	dg	vH	H	vL
20120-33-6	F	F	M	H	dg	M	M	L	M	M	vL
1779-48-2	C	C	M	M	M	M	L	L	L	H	vL
55566-30-8	F	F	H	L	H	H	M	H	vH	M	M
25155-23-1	F	F	L	L	H	H	L	M	H	H	L
791-28-6	C	C	M	dg	M	M	L	L	M	H	L
78-40-0	F	F	M	H	M	M	M	L	L	M	L
513-02-0	F	F	M	H	M	M	H	L	vH	vH	vH
513-08-6	B	B	M	M	M	M	L	M	M	L	vL
814-29-9	B	F	M	dg	dg	dg	L	M	M	L	L
995-32-4	B	F	M	M	dg	M	L	dg	dg	L	vL
2528-38-3	C	C	L	M	M	M	L	dg	vH	L	vL
9006-37-5	F	F	M	dg	M	dg	M	dg	dg	dg	dg
1754-47-8	F	F	M	dg	dg	M	L	H	H	M	M
78-32-0	B	B	M	L	M	M	L	M	H	L	L
64532-95-2	F	F	L	L	M	M	L	M	vH	H	vH
68478-33-1	F	F	L	L	M	M	H	M	H	vH	vL
78-33-1			vH	L	M	M	L	M	H	vH	vL
64532-94-4	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
69515-46-4	B	B	L	L	M	M	L	M	H	L	L
55864-04-5	C	C	L	L	M	dg	M	M	H	L	H
96107-55-0	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
69500-29-4	C	C	L	L	M	M	L	M	H	H	vH
69500-30-7	B	C	L	L	dg	M	L	M	H	M	L
55864-07-8	C	C	L	M	M	M	M	dg	H	M	L
2190501-29-0	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
72668-27-0	C	C	L	M	M	M	M	dg	vH	H	M
2502-15-0	C	C	L	M	M	M	M	M	H	H	H
83242-23-3	C	C	L	M	M	M	M	M	H	H	vH
981-40-8	B	B	L	M	M	M	M	M	H	L	M
65652-41-7	C	C	vH	M	M	M	M	dg	H	H	M
115-87-7	C	C	L	M	M	M	M	dg	H	H	H
57583-54-7	C	C	L	M	L	L	M	M	M	H	L
5945-33-5	C	F	L	dg	dg	dg	L	dg	vH	H	M
4090-51-1	C	F	H	dg	dg	dg	L	M	vH	M	L
181028-79-5	C	C	vL	M	M	M	L	M	H	H	vL
225789-38-8	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
756-79-9	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
242-555-3	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
35948-25-5	B	B	L	M	L	M	M	M	H	M	vL
14852-17-6	F	F	L	dg	dg	dg	dg	dg	dg	dg	vL
28108-99-8	B	B	L	M	M	M	L	dg	H	L	vL
1003300-73-9	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
2781.11.5	B	B	M	L	L	L	M	M	L	M	L
77226-90-5	B	B	L	L	L	L	L	dg	L	vH	L
68664-06-2	C	C	L	M	L	L	L	dg	L	vH	H
68952-33-0	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
126-71-6	B	B	L	M	M	L	L	L	M	M	vL
139189-30-3	C	F	L	M	dg	dg	M	dg	M	vH	vL
46355-07-1	F	F	L	dg	dg	M	M	dg	H	H	vL
6161-81-5	B	C	L	M	M	dg	L	M	H	L	L
63562-34-5	B	F	M	dg	dg	M	L	dg	H	L	vL
803-19-0	C	F	M	dg	dg	M	L	dg	H	H	vL
78-36-6	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
813-76-3	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg

Organophosphate Flame Retardants
Heat Map

CAS #	Initial	Final	AT	C	R	D	M	E	AA	P	B
18755-43-6	F	F	M	M	H	H	L	dg	L	M	vL
115-89-9	B	C	M	L	dg	M	M	L	H	L	vL
61451-78-3	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
115-88-8	C	F	L	M	dg	dg	L	M	L	M	H
63562-33-4	B	F	L	dg	dg	M	L	dg	H	M	vL
41203-81-0	C	F	vH	dg	dg	M	L	dg	H	H	vL
53534-65-9	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
2528-39-4	B	F	L	dg	dg	M	M	dg	H	L	vL
1806-54-8	C	C	L	M	M	M	L	M	vH	M	vL
1067-12-5	F	F	L	H	dg	L	M	M	L	L	vL
72236-72-7	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
789440-10-4	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
3040-56-0	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg
1623-08-1	F	F	dg	dg	dg	dg	dg	dg	dg	dg	dg

Figure 13 OPFR Heat Map

Acute Mammalian Toxicity

Sixty-five percent of the assessed OPFRs received a Low or Moderate hazard score in our evaluations of acute mammalian toxicity (See Figure 14 and Table 13). However, very high and very low scores were seen for a small number of flame retardants. In general, the Low hazard scores were given based on empirical and predictive data while the Moderate hazard scores were assigned by authoritative sources. Out of the 97 chemicals assessed 15 had a hazard score of High or very-High; most of these were assigned based on empirical data.

Acute Mammalian Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	18					18
vL						
L		14	17	5	4	36
M		9	6	13		28
H		4	1	3		8
vH		5	1	1		7
Total	18	32	25	22	4	97

Table 12 Acute Mammalian Toxicity Data

Out of the 97 compounds tested, a total of 32 compounds had empirical data which is the largest number with empirical data for any endpoint. As per QCAT© guidance, the empirical data that were used came only from studies on rats and humans. Occasionally data from other species were found but were not used to assign a hazard score. When empirical data was utilized, the methodology mandated that oral, inhalation, and/or dermal LD50 values with the lowest LD50 values be used as the basis for the hazard score assigned (Stone, 2016).

Step 1 data sources that were used as the basis for the initial hazard score included public databases such as ChemHat, ECHA, and ChemIDplus (Safer Chemicals Database, 2018; U.S. National Library of Medicine, 2018; Union, 2018). Out of the 22 OPFR that received a grade designation from an authoritative source, most (60%) received a grade of Moderate. According to the ECHA H-Statements, a majority of the OPFR received "Harmful" designation which constituted a Moderate hazard score, and not "Fatal or Toxic" which would correlate to very-High or High hazard score respectively.

If Step 1 data sources and empirical data were unavailable, modeling software was used to predict the acute toxicity. Most notably, U.S. EPA's Toxicity Estimation Software Tool (T.E.S.T.), was used to predict rat oral LD_{50} values (US Environmental Protection Agency, 2018c). Of the 25 compounds designated based on predicted software, 17 were given a Low score and 6 were given a Moderate score. However, a much wider range of scores was predicted. For example, one compound, Bisphenol-A bis (diphenyl phosphate) (CAS # 181028-79-5), was given a Low score with a predicted 4287.35 mg/kg oral rat LD_{50} (from T.E.S.T) and a predicted LD_{50} of 2000 mg/kg from CompTox (US Environmental Protection Agency, 2018c, 2018b). In contrast, another compound, Phosphonic acid, (5-ethyl-2-methyl-2-oxido-1,3,2-dioxaphosphorinan-5-yl)methyl methyl ester (CAS # 41203-81-0), was given the predicted grade of very-High due to U.S. EPA's T.E.S.T. software's prediction of an oral rat LD_{50} of 49.97 mg/kg.

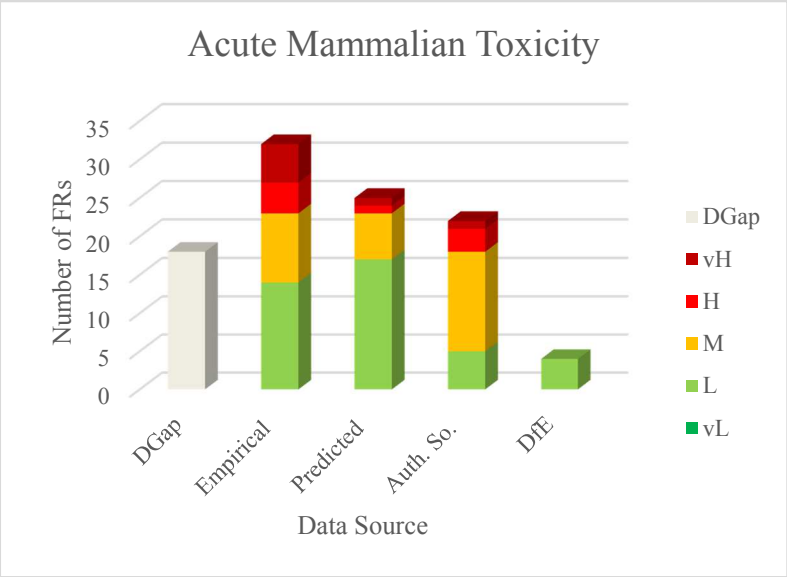


Figure 14 Acute Mammalian Toxicity Data

Carcinogenicity

Most OPFRs received hazard scores of Moderate for carcinogenicity. This is seen with an approximate even distribution of hazard scores between Low (20), Moderate (30) and High (13) hazard scores (See Figure 15 and Table 14). As indicated in Table X, the majority of Low and Moderate hazard scores came from prediction data while authoritative sources were the basis for a majority of High hazard scores.

Carcinogenicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	34					34
vL						
L		3	13	4	1	20
M		1	23	6	3	30
H		1	2	10		13
vH						
Total	34	5	38	20	4	97

Table 13 Carcinogenicity Data

Of the 97 chemicals assessed for carcinogenicity, there were a total of 35 identified data gaps due to a lack of empirical data (See Figure X and Table X). Of the remaining 62 compounds without data gaps, 5 had empirical data which supported the endpoint's initial grade.

Predictions were relied upon for 38 compounds for this endpoint. The predictions were generated by the Vega Cesear, ISS, IRFMN/Antares, and IRFMN/ISSCAN-CGX software models (Vegahub.eu, 2017). The majority of grades given based on predictions were Low and Moderate with only 2 OPFR (CAS # 6145-73-9, 13674-84-5) receiving a grade of High. There were several structural alerts for carcinogenicity identified which included:

- Alkyl (C<5) or benzyl ester of sulphonic or phosphonic acid
- epoxides and aziridines
- the isocyanate and isothiocyanate groups

The remaining 20 compounds were given grades based upon authoritative source listings, namely ECHA H-Statements and the California Prop 65 list (OEHHA, 2018; Union, 2018).

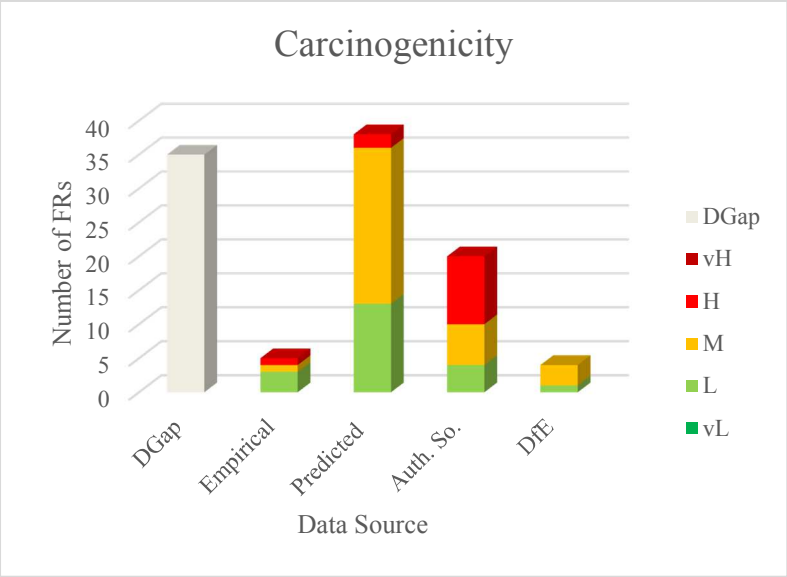


Figure 15 Carcinogenicity Data

Reproductive and Developmental Toxicity

The assigned Reproductive and Developmental Toxicity hazard scores range from Low to High. Overall most of the OPFRs exhibited Moderate Toxicity at these two endpoints, which is seen by 41 compounds and 56 compounds, respectively, receiving a moderate grade (See Figures 16, 17, and Tables 15, 16). For both endpoints, the moderate scores were largely assigned based on empirical and modeling data. However, a large number of data gaps were seen.

Reproductive Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	41					41
vL						
L		4	1	4	4	9
M		12	27	2		41
H				6		6
vH						
Total	41	16	28	12	4	97

Table 14 Reproductive Toxicity Data

Developmental Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	26					26
vL						
L		4	3	2	2	9
M		14	37	5	2	56
H		2		4		6
vH						
Total	26	20	40	11	4	97

Table 15 Developmental Toxicity Data

There were 41 data gaps identified for the Reproduction endpoint and 26 for Developmental Toxicity. The occurrence of substantially more data gaps for Reproductive Toxicity than for Developmental Toxicity was also seen in our previous evaluation of the OHFRs. (See Chapter 1)

Twelve compounds received scores based on Reproductive Toxicity based on authoritative sources while eleven were assigned based on Developmental. For both endpoints, the authoritative sources largely resulted in Moderate to High hazard scores. The majority of Moderate hazard scores assigned relied on both empirical data and prediction-based data.

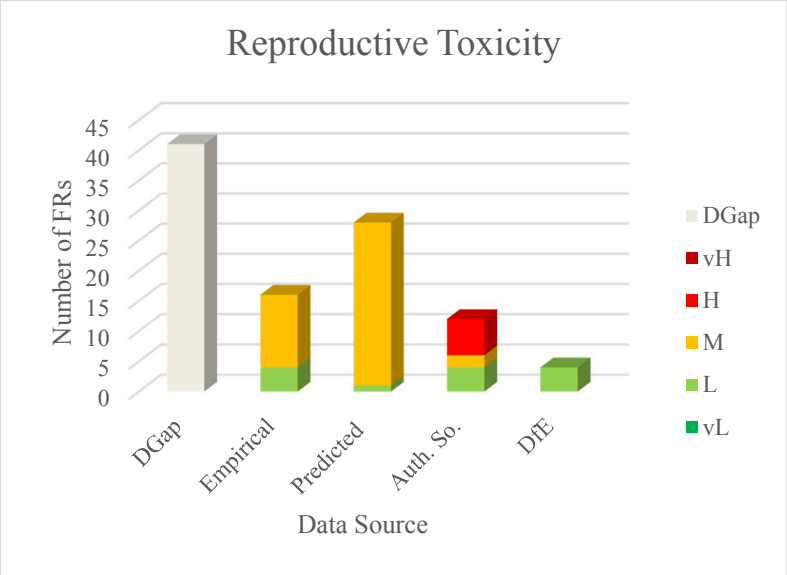


Figure 16 Reproductive Toxicity Data

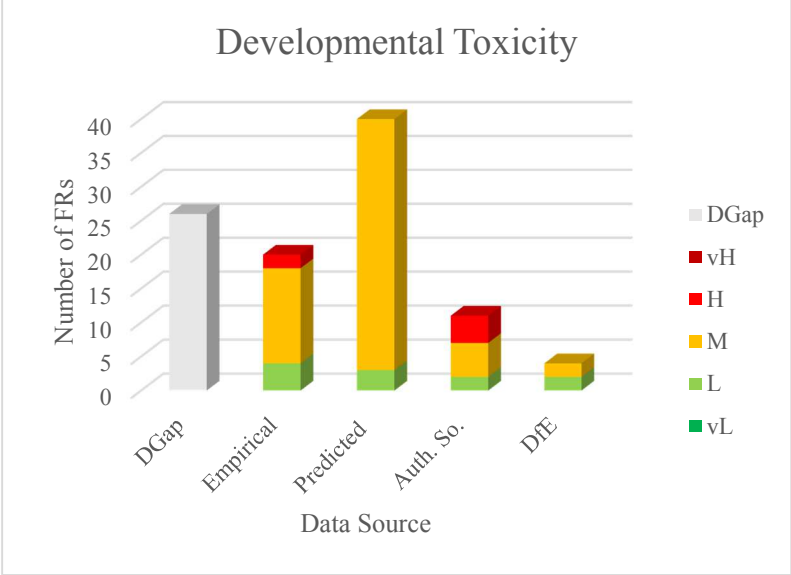


Figure 17 Developmental Toxicity Data

Mutagenicity and Genetic Toxicity

Overall, the evaluated OPFRs received Low to Moderate hazard scores for Mutagenicity and Genetic Toxicity with a skew towards Low (See Figure 18 and Table 17). Forty-one compounds received Low scores and twenty-nine received Moderate scores based primarily on empirical and predictive data sources.

Mutagenicity/ Genetic Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	20					20
vL						
L		14	24	3	3	41
M		11	14	4	1	29
H		3		4		7
vH						
Total	20	28	38	11	4	97

Table 16 Mutagenicity/Genetic Toxicity Data

Only 20 data gaps were identified from among the 97 OPFRs. In regards to predicted data, 24 compounds were predicted to have a hazard score of Low while 14 were given a hazard score of Moderate. Models were also used to identify structural alerts for *in vivo* or *in vitro* mutagenicity. From these prediction models, structural alerts were identified such as:

- Alkyl (C<5) or benzyl ester of sulphonic or phosphonic acid
- H-bond acceptor,
- 1-phenoxybenzene

There were 28 compounds graded using empirical data. There were some compounds that were negative for the *Salmonella* reverse mutation assays but positive in

other assays. For these select few compounds, a hazard score of Moderate was assigned based on the empirical data.

There were also 11 compounds given a grade designation due to authoritative sources such as ECHA H-Statements and various country's GHS statements (Authority, 2018; Evualuation, 2018; KOSHA Chemical Information, 2018).

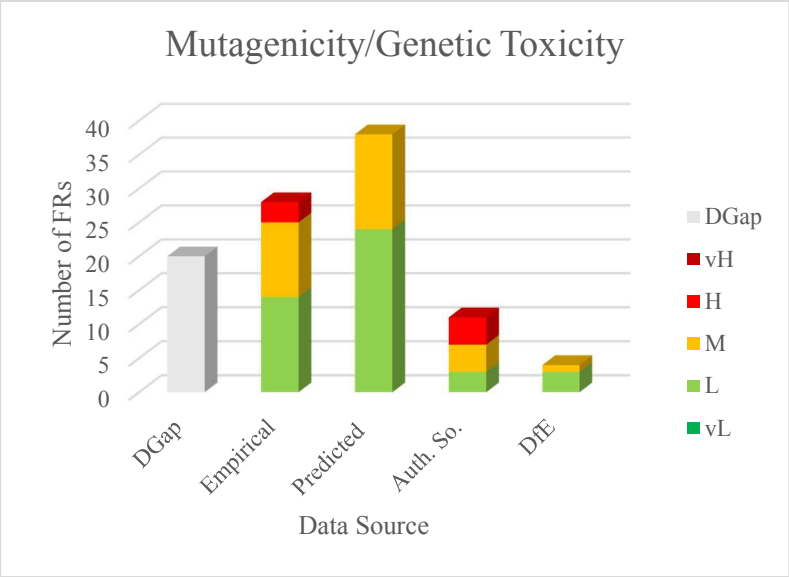


Figure 18 Mutagenicity/Genetic Toxicity Data

Endocrine Disruption

Overall, 29 compounds were given a Moderate hazard score (See Figure 19 and Table 18) with13 compounds assigned a Low score and 12 a High score. The majority of compounds, 43, were designated as having a data gap.

Endocrine Disruption	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	43					43
vL						
L		1	9	3		13
M		1	25	3		29
H		3	1	8		12
vH						
Total	43	5	35	14		97

Table 17 Endocrine Disruption Data

This endpoint had a total of 43 data gaps, which was more than any other endpoint. This stems at least in part from the lack of standardization in assessing this endpoint and a lack of consensus as to exactly what constitutes endocrine disruption (Hodgson, 2010).

Prediction software was used to determine this endpoint where applicable. The majority of the predictions came from Vega or Comptox (CERAPP) models (US Environmental Protection Agency, 2018a, 2018b; Vegahub.eu, 2017). These predictions accounted for 35% of the Endocrine Disruption data and the majority (72%) of the predictions received a Moderate score.

Several authoritative databases were also used to determine the hazard score for this endpoint. These included TEDX, the European Commission, and OSPAR (Safer Chemicals Database, 2018; Ted.com, 2018; Union, 2018). These databases

predominantly gave a designation of High, while there were 3 Moderate and 3 Low hazard scores assigned based on authoritative sources.

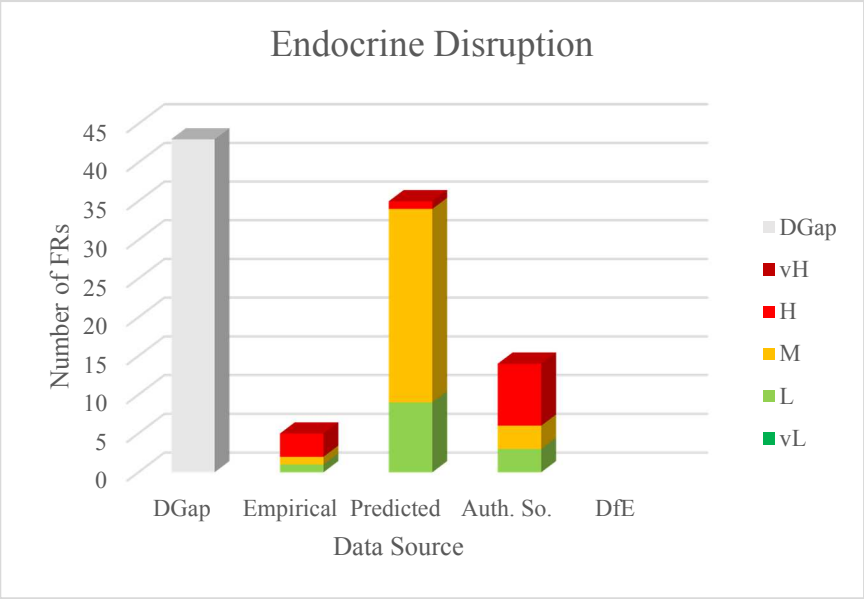


Figure 19 Endocrine Disruption Data

Acute Aquatic Toxicity

Overall just over half of the OPFRs (53 of the 97) received a hazard score of High or very-High (See Figure 20 and Table 19). In contrast, only 22 compounds received either a Low or Moderate score.

Acute Aquatic Toxicity	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	22					22
vL						
L		5	4	2	2	11
M		2	5	4		11
H		4	25	3	1	32
vH		2	10	9	1	21
Total	22	13	44	18	4	97

Table 18 Acute Aquatic Toxicity Data

There were a total of 22 data gaps designated for this endpoint and it also was the endpoint with the highest percentage of very-High and High graded compounds (52%). About half of the scores were determined by modeling software, namely T.E.S.T. and Vega (US Environmental Protection Agency, 2018c; Vegahub.eu, 2017) with approximately 80% of those receiving either a High or very-High hazard score.

The little empirical data identified were from studies done on a variety of aquatic species. Studies on fathead minnow and algae were found for 13 of the compounds. The 18 compounds which were scored based on authoritative sources relied mainly on GHS statements from countries such as Japan, Korea, and New Zealand (Authority, 2018; Evualuation, 2018; KOSHA Chemical Information, 2018). These sources primarily gave grades of very-High or High.

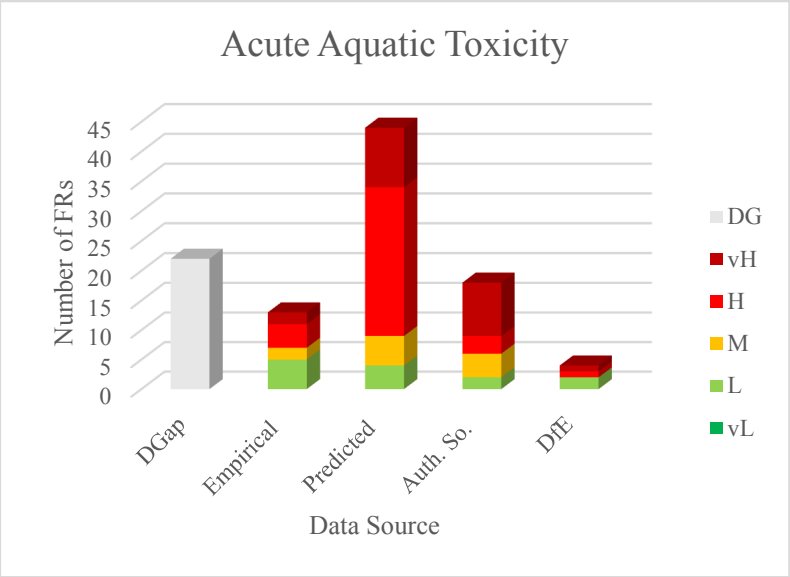


Figure 20 Acute Aquatic Toxicity Data

Persistence

The OPFRs evaluated received a broad range of hazard scores with approximately equal numbers receiving scores of very-High, High, Moderate and Low (See Figure 21 and Table 20). Twenty-one of the chemicals were designated as having data gaps and only one agent (CAS # 140-08-9) was identified as having empirical data. 55 of the 97 OPFRs received scores based on modeling predictions using software such as Vega and Epi-suite (US Environmental Protection Agency, 2012; Vegahub.eu, 2017). Of these predictions, an almost even distribution of scores occurred across High, Medium, and Low. There were 4 compounds with predictions of very-High. There was very little difference in the outcomes of the two prediction software platforms used.

Authoritative sources did provide a grade designation for 20 compounds with 16 of these receiving a very-High hazard score.

Persistence	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	21					21
vL						
L			15			15
M		1	18	3	2	22
H			18	1	1	19
vH			4	16	1	20
Total	21	1	55	20	4	97

Table 19 Persistence Data

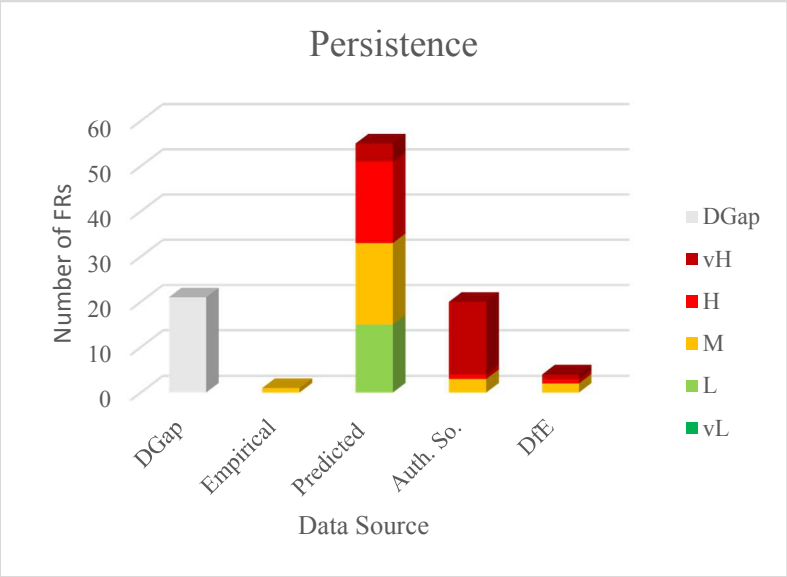


Figure 21 Persistence Data

Bioaccumulation

In general, our evaluation indicated little concern for bioaccumulation for the evaluated OPFRs with 33 compounds receiving a very-Low hazard score and 16 receiving a Low hazard score (See Figure 22 and Table 21). About half of the assigned hazard scores were based on software predictions using modeling software such as Epi-Suite, Vega, and T.E.S.T. (US Environmental Protection Agency, 2012, 2018c). 39 of the 97 OPFRs being predicted to have a Low or very-Low hazard score.

Bioaccumulation	*DGap*	*Empirical*	*Predicted*	*Auth. So.*	*DfE*	*Total*
DGap	20					20
vL		5	25	3	2	33
L		1	14	1		16
M		2	5	2	2	9
H		2	4	4		10
vH		1	3	5		9
Total	20	11	51	15		97

Table 20 Bioaccumulation Data

A total of 20 compounds were designated as having a data gap. Fifteen were classified based on authoritative sources and 11 were from empirical data

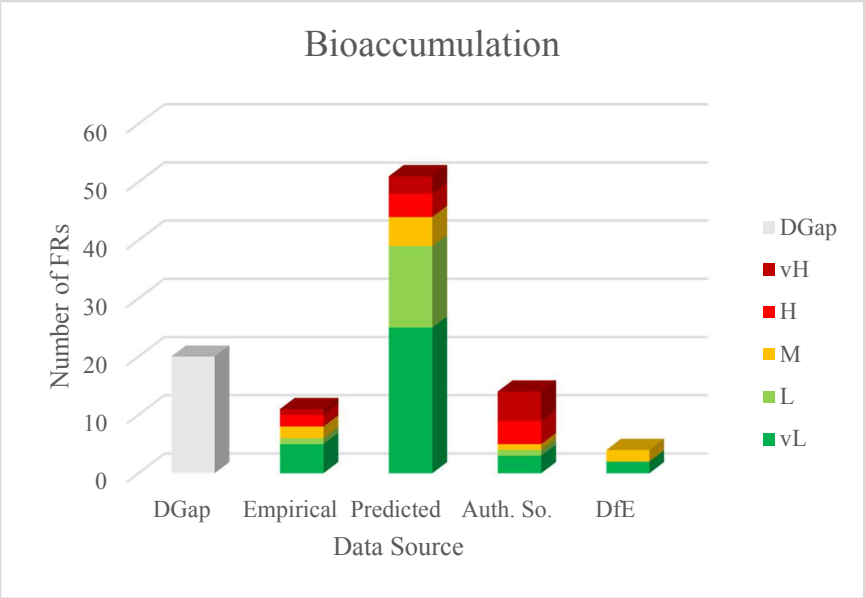


Figure 22 Bioaccumulation Data

GreenScreen®

GreenScreen® data were acquired where available. Of the 97 compounds assessed only one compound (2-Ethylhexyl diphenyl phosphate), besides the DfE compounds, had the data for all the required additional GreenScreen® endpoints. It received a failing grade using QCAT© so the chemical would not have gone forward for further evaluation using the sequential approach that we have proposed. If a complete investigation had been conducted to search and provide scores based on the GreenScreen® methodology, it is projected that only a small number of compounds may have received GreenScreen® grades. The following are the results from GreenScreen® methodology:

- 10 Neurotoxic
- 15 Respiratory Sensitive
- 11 Skin Sensitive
- 41 Corrosive/Irritation Skin
- 21 Systematic toxic
- 25 Chronic Aquatic Toxicity
- 16 Reactivity
- 17 Flammable

Of the 97 organophosphate flame retardants assessed using the additional GreenScreen® endpoints, 41 were given hazard scores for being corrosive/irritating to the skin while another 17 and 16 were deemed to be flammable or reactive, respectfully. Some flame retardants, specifically those that were classified as flammable/reactive, are flame resistant to a certain temperature or for a certain period of time. Once those two thresholds are breached during a fire then they can become quite flammable and produce

toxic gasses (Li et al., 2019; Luo, Bao, Guo, Li, & Zeng, 2016). About 10% of the evaluated flame retardants are also known to induce severe neurological effects, especially after repeated, long-term exposure. Other organophosphate compounds such as pesticides are known to cause neurological damage. Many of these flame retardants are also linked to chronic aquatic toxicity, which is not surprising since they were associated with Acute Aquatic Toxicity in our QCAT© screen.

General trends associated with the GreenScreen® assessment include designations of corrosive/skin irritants and systematic toxic as well as chronic aquatic toxicity.

Overall Assessment

In this study, the initial scores and Benchmark scores differed a moderate number of times. This can be seen in Table 22. The Initial scores are those given without consideration of any data gaps while the Final or Benchmark score is given with these data gaps in mind. There were 34 compounds that were initially given a grade of F while after the inclusion of data gaps this number increased roughly 40%. Of the 20 compounds initially given a grade of B half of them lost this designation when data gaps were considered.

	Scores	
	Initial	Final
F	34	48
C	27	23
B	20	10
A	0	0
DGap	16	16

Table 21 OPFR Hazard Scores

For OPFRs, there is a large amount of data that is currently unknown, unreported, or not accessible in the public databases to which we evaluated. This is highlighted in the fact that out of the 97 compounds investigated, there were at least 16 compounds that had data gaps for more than 4 endpoints giving them a final grade of F_{DG}. The average

number of Data Gaps for the given endpoints was 27 which corresponds to roughly one-quarter of the compounds investigated. This most prevalent for the endpoint, Endocrine Disruption, and Reproductive Toxicity, where about 40% of the compounds had a data gap (See Appendix 4).

Overall, prediction software was heavily relied upon for this assessment and accounted for 40% of the endpoint data in the heat map. Empirical data was available mainly for the Human Health endpoints such as Acute Toxicity and Mutagenicity/Genetic Toxicity and was unavailable for the Environmental endpoints such as Persistence and Bioaccumulation.

Discussion

A number of key observations can be made from our evaluation of the OPFRs. One is that large amounts of important toxicological information are unavailable for this class of compounds. As reported in Chapter 1, we previously conducted assessments of over 90 halogenated flame retardants and saw a minimum of 2 data gaps for any given endpoint while the 97 organophosphate flame retardants had a minimum of 14 data gaps for any endpoint. This indicates the in lack of toxicological testing and data on the organophosphate flame retardants as a class.

One major flaw in the QCAT© process for this class of compounds is that it does not consideration neurotoxicity. Phosphates as a class are known for their neurological toxicity and systematic toxicity. These are evaluated in the GreenScreen® process and not in the QCAT© method (Anastas, Heine, & Whittaker, 2018; Scr, 2016; Stone, 2016).

This means that many known and prominent toxicants such as Tri-o-cresyl phosphate (78-30-8) and Tris (3-isopropylphenyl) phosphate (72668-27-0) are given passing grades in the QCAT© evaluation since these types of toxicity are not considered in the QCAT© process. This also supports the idea that QCAT© should be a first pass assessment and that compounds receiving grades of C or better that are to be used widely, should then be assessed the more comprehensive GreenScreen® method. For the OPFRs, we compiled data to apply the GreenScreen® methodology for select compounds which had received passing grades in our QCAT© evaluation such as Tris (3-isopropylphenyl) phosphate (72668-27-0). These quickly failed the GreenScreen® process for either being too toxic or having too many data gaps.

Looking at the averages for the basis of the hazard scores, Authoritative Sources, Predictions, Empirical data, and DfE, it is readily apparent that the majority of the data acquired came from modeling predictions (See Appendix 4). The reliance on predictive data for this class of compounds somewhat concerning as the reliability of the model predictions for this class of chemicals is unknown. Empirical data should be generated for these endpoints to verify if modeling predictions are accurate.

It should be noted that QCAT© is a hazard assessment and does not take into account exposure or risk. Since, QCAT© requires substantial less data compared to GreenScreen®, it is inherently less thorough and reliable. Final decisions should be based on a full hazard assessment in conjunction with an evaluation of exposure and risk.

Notable Organophosphates and Impacts

Our assessment included some notable organophosphates that are currently within circulation (See Table 23). The majority of these compounds received a failing grade from the QCAT© assessment. Table 23 shows if the compounds have had a previous GreenScreen® or DfE assessment completed.

CAS #	*Final Grade*	*GreenScreen®?*	*DfE?*
78-42-2	F	No	No
78-51-3	F	No	No
115-86-6	F	Yes, 2	No
115-96-8	F	Yes, 1	No
126-73-8	F	No	No
1330-78-5	F	No	No
13674-87-8	F	Yes, 1	No
55566-30-8	F	Yes, 2	No
513-08-6	B	No	No
126-71-6	B	No	Yes
1241-94-7	F	No	No
78-30-8	C	Yes, 1	No
77226-90-5	B	Yes, 2	Yes
225789-38-8	F	Yes, 2	No
181028-79-5	C	Yes, unavailable	No

Table 22 GreenScreen® and DfE Scores

For the compounds that have been assessed by the GreenScreen® method, their Benchmark grades are noted. The highest GreenScreen® Benchmark grade received was a 2 for "Use but Search for Safer Substitutes" while others received Benchmark scores of 1 for "Avoid – Chemical of High Concern." For Poly[phosphonate-co-carbonate (CAS *77226-90-5),* which received a B using the QCAT© method, received a Benchmark Score of 2 in the GreenScreen® assessment (Rosenblum & Stone, 2016). Even with this passing grade, it should be noted that this compound received a Data Gap notation for the Endocrine Disruption endpoint and very-High hazard score for Persistence; the rest of the QCAT© endpoints were assigned a Low hazard score. In a previously published GreenScreen® assessment, this compound received a Data Gap score for neurological

toxicity (single dose), systematic toxicity (single dose), and respiratory irritant endpoints (Rosenblum & Stone, 2016). The GreenScreen® assessment did give this compound a Low hazard score for Endocrine Disruption, a determination which was based on limited bioavailability and SF polymer assessment guidance from the EPA's Alternative Assessment (Rosenblum & Stone, 2016). Out of all 97 compounds that we evaluated, Poly [phosphonate-co-carbonate] was the most non-toxic of the flame retardant even though it still received a very-High hazard score of persistence from both assessments and had a number of Data gaps in the GreenScreen® assessment.

The Final QCAT© scores do correlate well with the Benchmark scores given through the GreenScreen® method. This is not surprising in that the two methods measure many of the same endpoints. However, this confirms the reliability of the QCAT© method and also supports the assertion that QCAT© should be used as a first pass assessment method. The five compounds evaluated (CAS 115-86-6, 115-96-8, 13674-87-8, 55566-30-8, 225789-38-8) in our QCAT© assessment and that received a passing Benchmark grade, ultimately received unfavorable GreenScreen® grades. The use of the QCAT© screen before performing the GreenScreen® would be more efficient and would save time and effort which could be used to look for other possible alternatives.

Organophosphates as Replacements

As noted previously, organophosphate flame retardants are starting to be used as replacements for halogenated flame retardants. This stems from California State and the US Consumer Product Safety Commission decisions to phase out halogenated flame retardants from many consumer products (Bloom & Kalra, 2018; Consumer Product Safety Commission, 2017).

In comparing the two classes of flame retardant, the only endpoint that showed measurable improvement in toxicity for the OPFR was the Bioaccumulation endpoint, which it should be noted, relied heavily upon modeling predictions. On average, both halogenated and organophosphate flame retardants received similar numbers of hazard scores for each endpoint (See Table 24). The notable difference being the Data Gap designation which was much more common in the organophosphate flame retardants evaluations, meaning there is less known about the organophosphates as compared to the halogenated flame retardants.

Hazard Score/Class	*Average # of Halogenated FR*	*Average # of Organophosphate FR*
very-Low	1	4
Low	20	19
Moderate	28	29
High	18	13
very-High	18	7
DGap	6	27

Table 24 OHFR and OPFR Average Scores

These minor differences in the number of hazard scores for each class did not prove to be significant. By comparing each of the halogenated flame retardants endpoints to the corresponding organophosphate flame retardant endpoints using the nonparametric Wilcox test, it was shown that there was no significant difference in the hazard scores between the two classes of flame retardant (See Appendix

5). The conclusion that there is no significance between the grade distributions for the two classes means that their overall relative hazards are not significantly different. Since hazard scores are linked to toxicity it suggests that the relative toxicities of the two classes are similar (See Chapter 1).

The large number of failing or low QCAT© and GreenScreen® scores indicates that the organophosphate class of chemicals should be more thoroughly evaluated before used as replacements for the halogenated flame retardants. As shown above, the most commonly used organophosphate flame retardants (See Table 23) did not receive a favorable score using both the QCAT© and the GreenScreen® assessments. This strengthens the contention that these chemicals should be treated as a class and not on an individual chemical basis.

References – Chapter 2

Anastas, P. T., Heine, L., & Whittaker, M. H. (2018). How Chemical Hazard Assessment in Consumer Products Drives Green Chemistry. In *Handbook of Green Chemistry*. https://doi.org/10.1002/9783527628698.hgc131

Aschberger, K., Campia, I., Pesudo, L. Q., Radovnikovic, A., & Reina, V. (2017). Chemical alternatives assessment of different flame retardants – A case study including multi-walled carbon nanotubes as synergist. *Environment International*, *101*, 27–45. https://doi.org/10.1016/j.envint.2016.12.017

Authority, E. P. (2018). *Chemical Classification and Information Database*. Retrieved from https://www.epa.govt.nz/database-search/chemical-classification-and-information-database-ccid/

Bloom, R., & Kalra, A. An act to add Article 5.5 (commencing with Section 19100) to Chapter 3 of Division 8 of the Business and Professions Code, relating to business. (2018). Sacarmento: California State Legislature. Retrieved from https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201720180AB2998

Blum, A. (2018). Green Science Policy Institute. Berkeley: Green Science Policy Institute.

Blum, A., & Ames, B. N. (1977). Flame-retardant additives as possible cancer hazards. *Science*, *195*(4273), 17. https://doi.org/10.1126/science.831254

Blum, A., Daley, R., & Babrauskas, V. (2011). Regulatory policy leading to halogenated flame retardants in furniture and baby products: fire safety and health concerns. *Organohalogen Compounds*, *73*, 2032–2035.

Canadian Substances Registry (DSL). (2018). Retrieved from https://pollution-waste.canada.ca/substances-search/Substance?lang=en

Consumer Product Safety Commission. (2017). Guidance Document on Hazardous Additive, Non-Polymeric Organohalogen Flame Retardants in Certain Consumer Products.

Deutsche, & Forschungsgemeinschaft. (2018). *List of MAK and BAT Values*. Retrieved from https://onlinelibrary.wiley.com/doi/pdf/10.1002/9783527812127

Evaluation, N. I. of T. and. (2018). *Japan GHS Classification*. Retrieved from http://www.safe.nite.go.jp/english/ghs/all_fy_e.html

Hodgson, E. (2010). *A Textbook of Modern Toxicology* (4th ed.). Hoboken, New Jersey: John Wiley & Sons, Inc.

KOSHA Chemical Information. (2018). *GHS Classification/Labeling-Korea*. Retrieved from https://msds.kosha.or.kr/kcic/english/msdssearch.do?listType=msds#n

Li, T.-Y., Bao, L.-J., Wu, C.-C., Liu, L.-Y., Wong, C., & Zeng, E. (2019). Organophosphate flame retardants emitted from thermal treatment and open burning of e-waste. *Journal of Hazardous Materials*, *367*, 390–396.

Luo, P., Bao, L. J., Guo, Y., Li, S. M., & Zeng, E. Y. (2016). Size-dependent atmospheric deposition and inhalation exposure of particle-bound organophosphate flame retardants. *Journal of Hazardous Materials*. https://doi.org/10.1016/j.jhazmat.2015.09.014

NCBI. (2018). PubMed. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/

OEHHA. (2018). *Proposition 65*. Retrieved from https://oehha.ca.gov/proposition-65/proposition-65-list

Paules, R. (2018). *Toxicology in the 21st Century (Tox21)*. Retrieved from https://ntp.niehs.nih.gov/results/tox21/index.html

Rosenblum, E., & Stone, A. (2016). GreenScreen ® Assessment for Polyphosphonate-co-carbonate, (October 2014).

Rstudio Team. (2016). RStudio: Integrated development for R. RStudio, Inc., Boston MA. *RStudio*. https://doi.org/10.1007/978-3-642-20966-6

Safer Chemicals Database. (2018). Chemical Hazard and Alternatives Toolbox-ChemHat). Retrieved from http://www.chemhat.org/en/about-chemhat/who-made-chemhat

Scr, E. N. (2016). GreenScreen for Safer Chemicals Hazard Assessment Guidance, *3*(March). Retrieved from http://www.greenscreenchemicals.org/static/ee_images/uploads/resources/1_GreenScreen_Guidance_v13_2016_3_8.pdf

Stapleton, H. M., Klosterhaus, S., Keller, A., Ferguson, P. L., Van Bergen, S., Cooper, E., … Blum, A. (2011). Identification of flame retardants in polyurethane foam collected from baby products. *Environmental Science and Technology*, *45*(12), 5323–5331. https://doi.org/10.1021/es2007462

Stone, A. (2016). *Quick Chemical Assessment Tool Version 2.0*. Olympia, Washington: Department of Ecology-Washington State.

Tamhane, A., & Gou, J. (2017). Advances in p-Value Based Multiple Test Procedures. *Journal of Biopharmaceutical Statistics*, *28*(1), 10–27.

Team, R. D. C., & R Development Core Team, R. (2016). R: A Language and Environment for Statistical Computing. *R Foundation for Statistical Computing*. https://doi.org/10.1007/978-3-540-74686-7

Ted.com. (2018). TEDX. The Endocrine Disruption Exchange. Retrieved from https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list

U.S. National Library of Medicine. (2018). ChemIDplus. Bethesda: ToxNet. Retrieved

from https://chem.nlm.nih.gov/chemidplus/

Union, E. (2018). *ECHA*. Retrieved from https://echa.europa.eu/information-on-chemicals/registered-substances

US Environmental Protection Agency. (2012). EPI Suite™-Estimation Program Interface. Environmental Protection Agency. Retrieved from https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

US Environmental Protection Agency. (2018a). Collaborative Estrogen Receptor Activity Prediction Project. Retrieved from https://comptox.epa.gov/dashboard/chemical_lists/CERAPP

US Environmental Protection Agency. (2018b). Comptox. Retrieved from https://comptox.epa.gov/dashboard

US Environmental Protection Agency. (2018c). Toxicity Estimation Software Tool (TEST). US Environmental Protection Agency. Retrieved from https://www.epa.gov/chemical-research/toxicity-estimation-software-tool-test

US Environmental Protection Agency. (2018d). US ChemView. Retrieved from https://chemview.epa.gov/chemview

van I, der V., & de, B. J. (2012). Phosphorus flame retardants: properties, production, environmental occurrence, toxicity and analysis. *Chemosphere*, *88*(1879–1298 (Electronic)), 1119–1153.

Vegahub.eu. (2017). VEGA. Retrieved from https://www.vegahub.eu/

Wei, G. L., Li, D. Q., Zhuo, M. N., Liao, Y. S., Xie, Z. Y., Guo, T. L., … Liang, Z. Q. (2015). Organophosphorus flame retardants and plasticizers: Sources, occurrence, toxicity and human exposure. *Environmental Pollution*. https://doi.org/10.1016/j.envpol.2014.09.012

Wilcoxon, F. (1950). SOME RAPID APPROXIMATE STATISTICAL PROCEDURES.

Annals of the New York Academy of Sciences. https://doi.org/10.1111/j.1749-6632.1950.tb53974.x

Windham, G. C., Pinney, S. M., Voss, R. W., Sjödin, A., Biro, F. M., Greenspan, L. C., … Kushi, L. H. (2015). Brominated flame retardants and other persistent organohalogenated compounds in relation to timing of puberty in a longitudinal study of girls. *Environmental Health Perspectives*. https://doi.org/10.1289/ehp.1408778

General Conclusion

The QCAT© method was used as an initial toxicological assessment to determine the overall toxicity of flame retardants. It was first applied to the halogenated flame retardants and then used to assess general patterns of toxicity on organophosphate flame retardants. Halogenated flame retardants are in the process of being phased out of many consumer products and are often being replaced by the organophosphate class. We decided to look at both classes to compare their general toxicities and to determine if the organophosphates are less toxic. It was found that other than being less bioaccumulative, as a class, the organophosphates did not appear to be significantly less toxic than the halogenated flame retardants. General patterns of toxicity were found using the QCAT© assessment. A GreenScreen® assessment was then attempted on the organophosphate flame retardants to determine if there was indeed publicly accessible information which could result in a full and completed assessment. It was found that there was not enough publicly available information to assess the majority of the organophosphate flame retardants using the GreenScreen® method. The limited number of organophosphate flame retardants that have had completed GreenScreen® assessments were given Benchmarks of 1 or 2. Benchmark scores of 1 and 2 are associated with toxic and hazardous chemicals and it is recommended that alternatives be used as a replacement for chemicals that receive these scores. Considering these organophosphate flame retardants are the replacements, it will be necessary to undertake a deeper analysis of these flame retardants to fully understand their toxicity as a class and find suitable substitutions. As indicated above, the QCAT methodology does not take into account potential for

exposure which could greatly influence the recommendation of the usage of each individual compound. It is recommended that a full and systematic evaluation (See Chapter 1, Appendix 3) be conducted with a consideration of likely exposures and risk before a final regulatory decision be made.

Comparing the QCAT© assessments of halogenated and organophosphate flame retardants allows a number of patterns to be seen. The Endocrine Disruption and Reproductive Toxicity endpoints have the highest amount of data gaps in both assessments. At first glance, it is apparent that the Bioaccumulation endpoint was significantly less toxic overall for the organophosphates than for the halogenated flame retardants. When looking at the areas in which high numbers of prediction were used and those with an overabundance of data gaps, it is clear that organophosphate flame retardants are not significantly less toxic than the halogenated flame retardants. After statistical analysis using Wilcox T-test and Bonferroni's multiple comparison adjustment, it was found that there was no significance between the toxicity of halogenated or organophosphate flame retardants (Tamhane & Gou, 2017; Wilcoxon, 1950). Since it has been proven and enforced through legislation that halogenated flame retardants are toxic and, according to this research, organophosphate flame retardants are not less non-toxic, the replacement of halogenated flame retardants with organophosphate flame retardants may not be warranted.

The data gathered does show the need for further investigation of classes of chemicals. Out of all the 90 halogenated and 97 organophosphate flame retardants evaluated, none received a QCAT© grade of A or B and a passable GreenScreen® score

(Benchmark score 3 or 4). Fewer than 5 of the 97 organophosphate compounds had enough publicly available data to successfully complete a GreenScreen® assessment.

Instead of individually testing each flame retardant for its toxicity, assessment tools such as QCAT© allow scientists to see general patterns of toxicity for entire classes. It also allows for the distillation of hundreds of compounds to a list of the top non-toxic chemicals which then can be evaluated with more extensive methods such as GreenScreen®. To our knowledge, this type of systematic evaluation of a class of chemicals has not previously been undertaken. This novel method has been shown to be efficient and successful at assessing chemicals as a class. By using this systematic approach to inform regulatory decisions, this should allow only the least toxic flame retardants or other chemicals of interest to be used. This approach can be a means to further protect both human and environmental health.

Anastas, P. T., Heine, L., & Whittaker, M. H. (2018). How Chemical Hazard Assessment in Consumer Products Drives Green Chemistry. In *Handbook of Green Chemistry*. https://doi.org/10.1002/9783527628698.hgc131

Aschberger, K., Campia, I., Pesudo, L. Q., Radovnikovic, A., & Reina, V. (2017). Chemical alternatives assessment of different flame retardants – A case study including multi-walled carbon nanotubes as synergist. *Environment International*, *101*, 27–45. https://doi.org/10.1016/j.envint.2016.12.017

Bloom, R., & Kalra, A. An act to add Article 5.5 (commencing with Section 19100) to Chapter 3 of Division 8 of the Business and Professions Code, relating to business. (2018). Sacramento: California State Legislature. Retrieved from https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201720180AB2998

Blum, A., & Ames, B. N. (1977). Flame-retardant additives as possible cancer hazards. *Science*, *195*(4273), 17. https://doi.org/10.1126/science.831254

Consumer Product Safety Commission. (2017). Guidance Document on Hazardous Additive, Non-Polymeric Organohalogen Flame Retardants in Certain Consumer Products.

Gold, M. D., Blum, A., & Ames, B. N. (1978). Another flame retardant, tris-(1,3-dichloro-2-propyl)-phosphate, and its expected metabolites are mutagens. *Science*, *200*(4343), 785–787. https://doi.org/10.1126/science.347576

Scr, E. N. (2016). GreenScreen for Safer Chemicals Hazard Assessment Guidance, *3*(March). Retrieved from http://www.greenscreenchemicals.org/static/ee_images/uploads/resources/1_GreenScreen_Guidance_v13_2016_3_8.pdf

Stone, A. (2016). *Quick Chemical Assessment Tool Version 2.0*. Olympia, Washington:

Department of Ecology-Washington State.

Tamhane, A., & Gou, J. (2017). Advances in p-Value Based Multiple Test Procedures. *Journal of Biopharmaceutical Statistics*, *28*(1), 10–27.

Wilcoxon, F. (1950). SOME RAPID APPROXIMATE STATISTICAL PROCEDURES. *Annals of the New York Academy of Sciences*. https://doi.org/10.1111/j.1749-6632.1950.tb53974.x

Appendixes

Chapter 1 Appendixes

Appendix 1: List of Halogenated Flame Retardants of Interest

CHEMICAL NAME	*ABBR.*	*CAS #*
1h-indene, 4,5,6,7-tetrabromo-2,3-dihydro-1,1,3-trimethyl-3-(2,3,4,5-tetrabromophenyl)-	OBTMPI	1084889-51-9, 893843-07-7, 1025956-65-3
Benzene, 1,1'-oxybis [2,3,4,5,6-pentabromo- or decabromodiphenyl ether	DecaBDE	1163-19-5
Phenol, 2,4,6-tribromo-	TBP	118-79-6
Phenol, 2,4,6-tribromo-3-(tetrabromopentadecyl)-	TBPD-TBP	168434-45-5
Benzene, 1,2,4,5-tetrabromo-3,6-dimethyl-	TBX	23488-38-2
1,3,5-triazine, 2,4,6-tris(2,4,6-tribromophenoxy)-	TBP-TAZ	25713-60-4
Tftr5r6	DBS	31780-26-4
1,4,-bis(2,4,6-tribromophenoxy)-2,3-dibromobutene	OBPB	31977-87-4
Pentabromodiphenyl ether	Penta BDE	32534-81-9
Octabromodiphenyl ether	Octa BDE	32536-52-0
N-n-ethylene-bis(tetrabromophthalimide	EBTEBPI	32588-76-4
Benzene, 1,3,5-tribromo-2-(2-propen-1-yloxy)-	TBP-AE	3278-89-5
Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, 1,1'-diacetate	TBBPA-BOAc	33798-02-6
Bicyclo[2.2.1]hept-2-ene, 1,2,3,4,7,7-hexachloro-5-(2,3,4,5-tetrabromophenyl)-	HCTBPH	34571-16-9
Benzene, 1,3,5-tribromo-2-(2,3-dibromopropoxy)-	TBP-DBPE	35109-60-5
Benzene, 1,2,3,4,5-pentabromo-6-(2-propen-1-yloxy)-	PBP-AE	3555-11-1
1,2-bis(2,4,6-tribromophenoxy)ethane	BTBPE	37853-59-1
Benzene, 1,2,3,4,5-pentabromo-6-(bromomethyl)-	PBBB	38521-51-6
Benzene, 1,2,3,4-tetrabromo-5-chloro-6-methyl-	TBCT	39569-21-6
Phenol, 4,4'-sulfonylbis[2,6-dibromo-	TBBPS	39635-79-5

Benzene, 1,1'-sulfonylbis[3,5-dibromo-4-(2,3-dibromopropoxy)- aka tetrabromobisphenol s	TBBPS-BDBPE	42757-55-1
Benzene, 1,1'-[oxybis(methylene)]bis[2,3,4,5,6-pentabromo- (9ci) cas/smile not found	DBDBE	497107-13-8
1,3,5-triazine-2,4,6(1h,3h,5h)-trione, 1,3,5-tris(2,3-dibromopropyl)-	TDBP-TAZTO	52434-90-9
1,3,5-triazine-2,4,6(1h,3h,5h)-trione, 1-(2,3-dibromopropyl)-3,5-di-2-propen-1-yl	DBP-TAZTO	57829-89-7
Benzene, 1,2,3,4,5-pentabromo-6-(chloromethyl)-	PBBC	58495-09-3
Benzene, 1,2,4,5-tetrabromo-3,6-bis(2,3,4,5,6-pentabromophenoxy)-	4′-PeBPOBDE208	58965-66-5
2-propenoic acid, (2,3,4,5,6-pentabromophenyl)methyl ester	PBB-Acr	59447-55-1
Phenol,2,3,4,5,6-pentabromo-	PBP	608-71-9
Phenol, 2,4-dibromo-	DBP	615-58-7
Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, polymer with 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxymethylene]]bis[oxirane]		68928-70-1 (polymer)
Benzene, 1,1'-sulfonylbis[3,5-dibromo-4-methoxy-	TBBPS-BME	70156-79-5
Tetrabromophthalic anhydride or 4,5,6,7-tetrabromo-2-benzofuran-1,3-dione (see cas 632-79-1 it is also tetrabromophthalic anyhdride,		72625-95-7
Decabromodiphenylethane	DBDPE	84852-53-9
Benzene, 1,2,3,4,5-pentabromo-6-ethyl-	PBEB	85-22-3
1,2,3,9-tetrabromo-1,2,3,4-tetrahydro-1,4-methanonaphthalene	TTMN	855992-98-2
1,2,3,9-tetrabromo-1,2,3,4-tetrahydro-1,4-methanonaphthalene	TTMN	855993-01-0
Benzene, 1,2,3,4,5,6-hexabromo-	HBB	87-82-1
Benzene, 1,2,3,4,5-pentabromo-6-methyl-	PBT	87-83-2
Brominated epoxy resin end-capped with tribromophenol		135229-48-0 (polymer)
Poly(dibromostyrene): benzene, ethenyl-, ar-bromo derivs., homopolymers (firemaster cp44-hf & pbs-64hw)		148993-99-1 (polymer)

Polypentabromobenzyl acrylate pbb-ma brominated polyacrylate or 2-propenoic acid, (2,3,4,5,6-pentabromophenyl)methyl ester, homopolymer		59447-57-3 (polymer)
Benzene, ethenyl-, homopolymer, brominated or brominated polystryene		88497-56-7 (polymer)
1-propanol, 2,3-dibromo-, 1,1',1''-phosphate	TDBPP	126-72-7
1-propanol, 3-bromo-2,2-bis(bromomethyl)-, 1,1',1''-phosphate	TTBNPP	19186-97-1
Tetrabromophthalic anhydride	TEBP-Anh	632-79-1
Bis(pentabromobenzyl) tetrabromophthalate	BPBTB	82001-21-6
Bis(pentabromobenzyl) terephthalate	BPBTerP	90075-91-5
Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester	EH-TBB	183658-27-7
1,2-benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) ester	HEEHP-TEBP	20566-35-2
1,2-benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester	BEH-TEBP	26040-51-7
1,3,5-triazine-2,4,6(1h,3h,5h)-trione, 1,3-bis(2,3-dibromopropyl)-5-(2-propen-1-yl)-	BDBP-TAZ	75795-16-3
1,2-benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, mixed esters with diethylene glycol and propylene glycol		77098-07-8
Tris(2-chloroethyl) phosphate	TCEP	115-96-8
Tris(1-chloro-2-propyl)phosphate	TCIPP	13674-84-5
2-propanol, 1,3-dichloro-, phosphate (3:1)	TDCIPP	13674-87-8 (see isomer 78-43-3)
Tetrakis(2-chloroethyl)dichloroisopentyldiphosphate or bis[bis(2-chloroethyl)phosphate] or phosphoric acid, p,p'-[2,2-bis(chloromethyl)-1,3-propanediyl] p,p,p',p'-tetrakis(2-chloroethyl) ester	BCMP-BBCP	38051-10-4
Tris(2,3-dichloro-1-propyl)phosphate		66108-37-0
2,3-dichloro-, 1,1,1-phosphate propanol	TDCPP	78-43-3 (see isomer 13674-87-8)
Cyclodecane, hexabromo-	HBCYD	25495-98-1

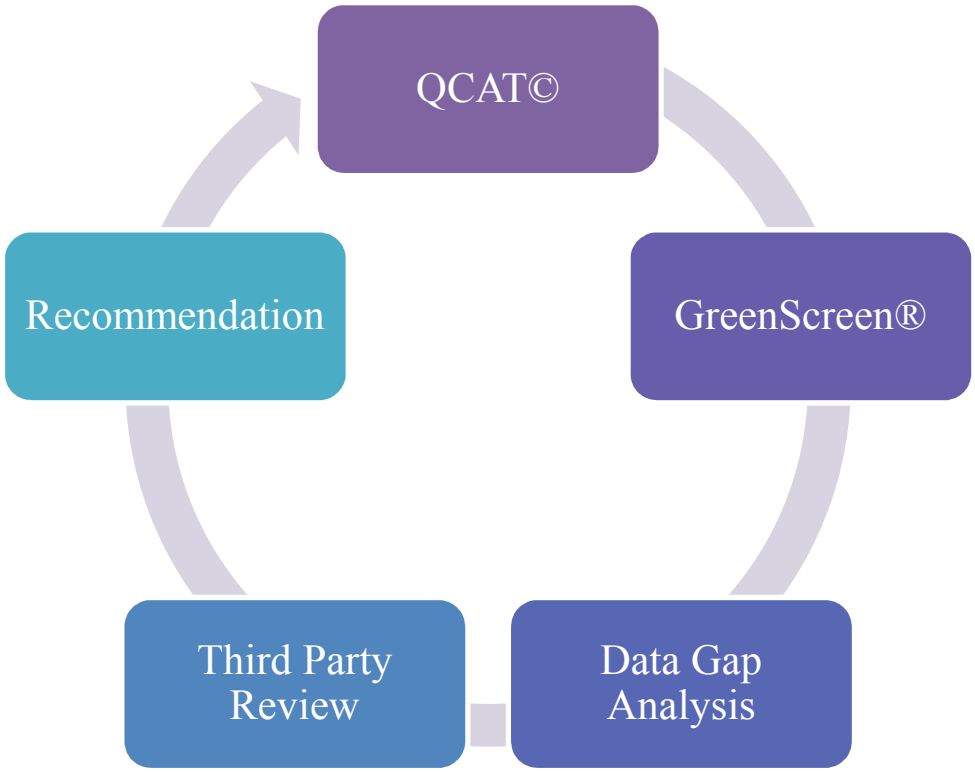
1,2,5,9,10-hexabromocyclodecane	unspecified HBCD	25637-99-4
1,2,5,9,10-hexabromocyclodecane	HBCDD	3194-55-6
Cyclooctane, 1,2,5,6-tetrabromo-	TBCO	3194-57-8
Cyclohexane, 1,2-dibromo-4-(1,2-dibromoethyl)-	DBE-DBCH	3322-93-8
Chlorendic anhydride aka 4,7-methanoisobenzofuran-1,3-dione, 4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro-	HCBCH-DCAnh	115-27-5
Chlorendic acid	HCBCH-DCA	115-28-6
1,4:7,10-dimethanodibenzo[a,e]cyclooctene, 1,2,3,4,7,8,9,10,13,13,14,14-dodecachloro-1,4,4a,5,6,6a,7,10,10a,11,12,12a-dodecahydro-	DDC-CO	13560-89-9
1,3,4-metheno-1h-cyclobuta[cd]pentalene, 1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-	MIREX	2385-85-5
1,4:6,9-dimethanodibenzofuran, 1,2,3,4,6,7,8,9,10,10,11,11-dodecachloro-1,4,4a,5a,6,9,9a,9b-octahydro-	DDC-DBF	31107-44-5
Hexachlorocyclopentadienyl-dibromocyclooctane	DBHCTD	51936-55-1
1-propanol, 3-bromo-2,2-bis(bromomethyl)-	TBNPA	1522-92-5
1,3-propanediol, 2,2-bis(bromomethyl) or 2,2-bis(bromomethyl)-1,3-propanediol	DBNPG	3296-90-0
1-propanol, 2,2-dimethyl-, tribromo derive. (tribromoneopentylalcohol)	TBPA	36483-57-5
Flamestab nor 116 or 1,3-propanediamine, n,n'-1,2-ethanediylbis-, reaction products with cyclohexane and peroxidized n-butyl-2,2,6,6-tetramethyl-4-piperidinamine-2,4,6-trichloro-1,3,5-triazine reaction products		191680-81-6
Alkanes, c10-13, chloro	SCCP	85535-84-8; 71011-12-6
Medium chain chlorinated paraffins	MCCP	85535-85-9

1,3-isobenzofurandione, 4,5,6,7-tetrachloro- (tetrachlorophthalic anhydride)	TCP-Anh	117-08-8
1,4:5,8:9,10-trimethanoanthracene, 1,2,3,4,5,6,7,8,12,12,13,13-dodecachloro-1,4,4a,5,8,8a,9,9a,10,10a-decahydro-	DDC-Ant	13560-92-4
Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2,3-dibromopropoxy)-	TBBPA-BDBPE	21850-44-2
Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-(2-propen-1-yloxy)-	TBBPA-BAE	25327-89-3
Oxirane, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxymethylene]]bis-	TBBPA-BGE	3072-84-2
Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo-, dipropanoate (9ci) no smile and cas is unknoen	TBBPA-BP	37419-42-4
Benzene, 1,1'-(1-methylethylidene)bis[3,5-dibromo-4-methoxy- aka tetrabromobisphenol a bme	TBBPA-BME	37853-61-5
Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis-	TBBPA-BHEE	4162-45-2
2-propenoic acid, 1,1'-[(1-methylethylidene)bis(2,6-dibromo-4,1-phenylene)] ester	TBBPA-BA	55205-38-4
2-propenoic acid, 1,1'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy-2,1-ethanediyl]] ester	TBBPA-BHEEBA	66710-97-2
Phenol, 4,4’-(-methylethylidene)bis[2,6-dibromo-]	TBBPA	79-94-7
1,2,5,9,10-hexabromocyclodecane	γ-HBCD	134237-52-8
1,2,5,9,10-hexabromocyclodecane	α-HBCD	34237-50-6
1,2,5,9,10-hexabromocyclodecane	β-HBCD	34237-51-7
2,2',4,4'-tetrabromodiphenyl ether	BDE-47	5436-43-1
Bis(2-ethylhexyl) tetrabromophthalate	BTB	26040-51-7

Appendix 2: OHFR Full Data Tables

Grade/Endpoint	*AT*	*C*	*R*	*D*	*M*	*E*	*AA*	*P*	*B*	*Averages*
vL	0	0	0	0	0	0	0	0	7	0.777778
L	38	21	15	21	46	2	32	0	8	20.333333
M	30	56	39	52	34	17	17	0	3	27.55556
H	14	11	16	15	5	53	15	4	27	17.777778
vH	6	0	0	0	1	0	24	85	44	17.777778
DGap	2	2	20	2	4	18	2	1	1	5.7777778
Total	90	90	90	90	90	90	90	90	90	
Data Type	*AT*	*C*	*R*	*D*	*M*	*E*	*AA*	*P*	*B*	*Averages*
Empirical	24	3	7	19	22	1	8	7	5	10.66667
Predicted	39	59	32	47	46	14	42	28	28	37.2222
Auth. So.	25	26	31	22	18	57	38	54	56	36.3333
DGap	2	2	20	2	4	18	2	1	1	5.77778
Total	90	90	90	90	90	90	90	90	90	

Appendix 3: Systematic Process Chart



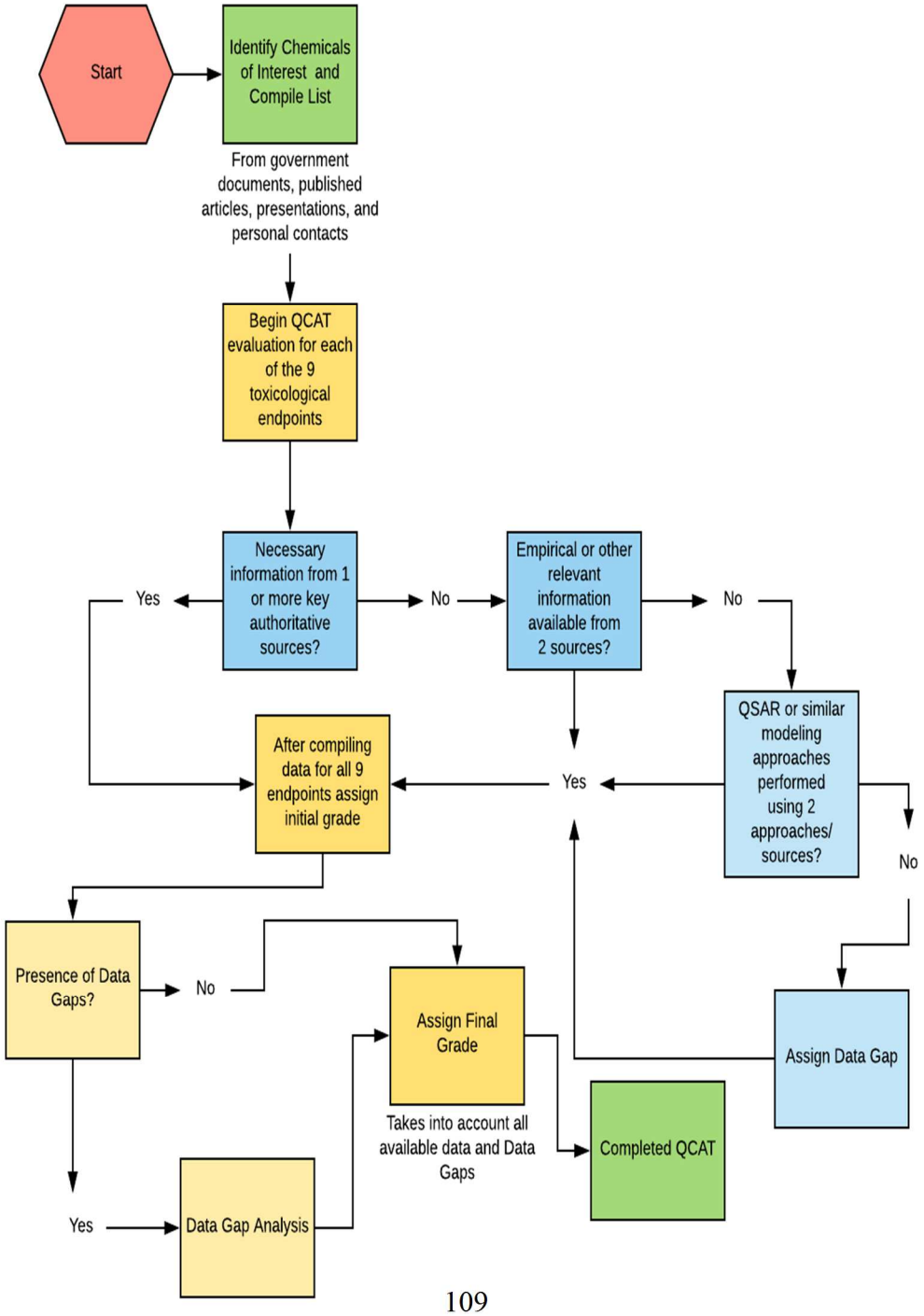
Appendix 4: OHFR Qualitative Data

The following link will take you to an excel file for the full QCAT© data assessed.

https://drive.google.com/open?id=1yAUHwjl3ku7N0AXZHwELAc2H9YxTNNnI

Chapter 2 Appendixes

Appendix 1: QCAT© Process Flow Chart



Appendix 2: Organophosphate Flame Retardants of Interest

Chemical Name	*CAS #*
Tris(2,3-Dibromopropyl) Phosphate	126-72-7
Tris(2-Butoxyethyl) Phosphate	78-51-3
Tris(2-Chloroethyl) Phosphate	115-96-8
Tris(2-Chloroethyl) Phosphite	140-08-9
Tris(2-Chloroisopropyl) Phosphate	13674-84-5
Tris(2-Chloropropyl) Phosphate	6145-73-9
Tris(2-Ethylhexyl) Phosphate	78-42-2
2-Ethylhexyl Diphenyl Phosphate	1241-94-7
Dimethyl Methylphosphate	756-79-6
Tris(1,3-Dichloro-2-Propyl)Phosphate	13674-87-8
Tricresyl Phosphate	1330-78-5
Triphenyl Phosphate	115-86-6
Trimethyl Phosphate	512-56-1
Tert-Butylphenyl Diphenyl Phosphate	56803-37-3
Triisopropylated Phenyl Phosphate	68937-41-7
Tributyl Phosphate	126-73-8
Tri-M-Tolyl Phosphate	563-04-2
Tri-O-Cresyl Phosphate	78-30-8
Sodium Triphosphate Hydrate (5:1:6)	15091-98-2
Sodium Polyphosphate	68915-31-1
O,O-Diethyl Chlorothiophosphate	2524-04-1
Isodecyl Diphenyl Phosphate	29761-21-5
Ethyltributylphosphonium Diethylphosphate	20445-94-7
Diphenyl Phosphate	838-85-7
Dimethyl Phosphate	813-78-5
Cresyl Diphenyl Phosphate	26444-49-5
2-Hydroxyethyl Methacrylate Phosphate	52628-03-2
Dimethyl Hydrogen Phosphite	868-85-9
Diethyl Ethylphosphonate	78-38-6
Dimethyl N-Methylolphosphonopropionamide	20120-33-6
Phenylphosphinic Acid	1779-48-2

Tetrakis(Hydroxymethyl)Phosphonium Sulfate	55566-30-8
Trixylyl Phosphate	25155-23-1
Triphenyphosphine Oxide	791-28-6
Triethyl Phosphate	78-40-0
Triisopropyl Phosphate	513-02-0
Tripropyl Phosphate	513-08-6
Tributylphosphine Oxide	814-29-9
Tetraethyl Ethylenediphosphonate	995-32-4
Tripentyl Phosphate	2528-38-3
Tris(3,5-Dimethyl Phenyl) Phosphate	9006-37-5
Dioctyl Phenylphosphonate	1754-47-8
Tri-P-Cresyl Phosphate	78-32-0
Tris(2-Isopropyl Phenyl) Phosphate	64532-95-2
Phenol, 2-(1-Methylethyl)-, Phosphate (3:1)	68478-33-1
Tris(4-Tert-Butylphenyl) Phosphate	78-33-1
2-Isopropylphenyl Diphenyl Phosphate	64532-94-4
3-Isopropylphenyl Diphenyl Phosphate	69515-46-4
4-Isopropylphenyl Dipheynyl Phosphate	55864-04-5
2,4-Diisopropylphenyl Diphenyl Phosphate	96107-55-0
Bis(2-Isopropylphenyl) Phenyl Phosphate	69500-29-4
Bis (3-Isopropylphenyl) Phenyl Phosphate	69500-30-7
Bis (4-Isopopylphenyl) Phenyl Phosphate	55864-07-8
Bis (2,4-Diisopropylphenyl) Phenyl Phosphate	2190501-29-0
Tris (3-Isopropylphenyl) Phosphate	72668-27-0
Tris (4-Isopropylphenyl) Phosphate	2502-15-0
2-Tert-Butylphenyl Diphenyl Phosphate	83242-23-3
4-Tert-Butylphenyl Diphenyl Phosphate	981-40-8
Bis (2-Tert-Butylphenyl) Phenyl Phosphate	65652-41-7
Bis (4-Tert-Butylphenyl) Phenyl Phosphate	115-87-7
Tetraphenylresorcinol Diphosphate	57583-54-7
2,2-Bis[4-[Bis(Phenoxy)Phosphoryloxy]Phenyl]Propane	5945-33-5
2,2-Oxybis[5,5-Dimethyl-1,3,2-Dioxaphosphorinane]2,2-Disulphide	4090-51-1

Bisphenol-A Bis (Diphenyl Phosphate)	181028-79-5
Diethylphosphinate, Aluminium Salt	225789-38-8
Dimethyl Methyl Phosphonate	756-79-9
Dimethyl Propane Phosphonate	242-555-3
Dopo - 9,10-Dihydro-9-Oxa-10-Phosphaphenanthren-10-Oxide	35948-25-5
Ethylenediamine-O-Phosphate Disconnected Structure	14852-17-6
Isopropyl Phenyl Diphenyl Phosphate	28108-99-8
Mixtures Of Esters Of Phosphoric Acid	1003300-73-9
N,N-(Bis)-Hydroxyethyl-Aminomethane Phosphonic Acid Diethyl Ester	2781-11-5
Polcarbonate-Polyphosphonate Copolymer	77226-90-5
Polyphosphonate Homopolymer / Oligomers	68664-06-2
Tar Acids, Cresylic, C8-Rich, Phosphates	68952-33-0
Tri-Iso-Butyl Phosphate	126-71-6
Resorcinol Bis[Di(2,6-Dimethylphenyl) Phosphate]	139189-30-3
Isopropyl Phenyl Phosphate	46355-07-1
Di-N-Octylphenyl Phosphate	6161-81-5
Bis(2-Hydroxyethyl) (6h-Dibenz[C,E][1,2] Oxaphosphorin-6-Ylmethyl)Succinate Poxide (65 Wt% In Ethylene Glycol)	63562-34-5
Bis(4-Carboxyphenyl)Phenylphosphine Oxide	803-19-0
Diethyl Ethyl Phosphonate	78-36-6
Diethylphosphinic Acid 3,9-Dihydroxy-,4,8,10-Tetraoxa-3,9- Diphosphaspiro[5,5]-Undecane-3,9-Dioxide	813-76-3
Dimethyl Propyl Phosphonate	18755-43-6
Diphenyl Methyl Phosphate	115-89-9
Hydroxymethylphenyl Phosphinic Acid	61451-78-3
Octyl Diphenyl Phosphate	115-88-8
[(6-Oxido-6h-Dibenz[C,E][1,2]Oxaphosphorin-6-Yl)-Methyl]-Butanedioic Acid	63562-33-4
Phosphonic Acid, Methyl(5-Methyl2-Methyl-1,3,2-Dioxaphosphorinan-5-Yl)	41203-81-0

Methyl,Methylester, P-Oxide P-Methoxyphenylhydroxymethylphosphinic Acid	
P-Methoxyphenyl-Phosphinic Acid	53534-65-9
Trihexyl Phosphate	2528-39-4
Trioctyl Phosphate	1806-54-8
Tris(Hydroxymethyl)Phosphine Oxide	1067-12-5
Bis(1,3-Dichloro-2-Propyl) Phosphate	72236-72-7
Bis(1-Chloro-2-Propyl) Phosphate	789440-10-4
Bis(2-Chloroethyl) Phosphate	3040-56-0
Dibenzyl Phosphate	1623-08-1

Appendix 3: List of Databases Used

Data Source	*Abbreviation*
ChemIDplus	
Safer Chemical Ingredients Safer List	
Hazardous Substances Data Bank (HSDB)	HSDB
Toxicology Literature Online (Toxline)	Toxline
Chemical Carcinogenesis Research Information System	CCRIS
Developmental And Reproductive Toxicology Database	Dart
Genetic Toxicology Data Bank	Gene-Tox
Integrated Risk Information System,	
International Toxicity Estimates For Risk	ITER
PubMed	
European Chemicals Agency	ECHA
High Production Volume Information System	HPVIS
Canadian Substances Registry	DSL
Chemical Hazard And Alternative Toolbox	Chemhat
Registry Of Toxic Effects Of Chemical Substances	RTECS
ChemView	
TEDX List Of Potential Endocrine Disrupters	TEDX
ToxCast	
14th Report On Carcinogens	
ToxNot	
German Mak List	
California Proposition 65 List	
Japan GHS Classification/Labeling	
New Zealand Ghs Classification/Labeling	
Korea GHS Classification/Labeling	
Collaborative Estrogen Receptor Activity Prediction Project	CERAPP
Modeling Software	
Mutagenicity (Ames Test) Consensus Model 1.0.2	Vega QSAR
Mutagenicity (Ames Test) Model (Caesar) 2.1.13	Vega QSAR
Mutagenicity (Ames Test) Model (Sarpy/Irfmn) 1.0.7	Vega QSAR
Mutagenicity (Ames Test) Model (Iss) 1.0.2	Vega QSAR
Mutagenicity (Ames Test) Model (Knn/Read-Across) 1.0.0	Vega QSAR
Carcinogenicity Model (Caesar) 2.1.9	Vega QSAR
Carcinogenicity Model (Iss) 1.0.2	Vega QSAR
Carcinogenicity Model (Irfmn/Antares) 1.0.0	Vega QSAR
Carcinogenicity Model (Irfmn/Isscan-Cgx) 1.0.0	Vega QSAR
Developmental Toxicity Model (Caesar) 2.1.7	Vega QSAR

Developmental/Reproductive Toxicity Library (Pg) 1.0.0	Vega QSAR
Estrogen Receptor Relative Binding Affinity Model (Irfmn) 1.0.1	Vega QSAR
Estrogen Receptor-Mediated Effect (IRFMN/CERAPP) 1.0.0	Vega QSAR
Skin Sensitization Model (Caesar) 2.1.6	Vega QSAR
Fish Acute (Lc50) Toxicity Classification (SARPY/IRFMN) 1.0.2	Vega QSAR
Fish Acute (Lc50) Toxicity Model (KNN/Read-Across) 1.0.0	Vega QSAR
Fish Acute (Lc50) Toxicity Model (NIC) 1.0.0	Vega QSAR
Fathead Minnow Lc50 96h (EPA) 1.0.7	Vega QSAR
Daphnia Magna Lc50 48h (EPA) 1.0.7	Vega QSAR
Daphnia Magna Lc50 48h (DEMETRA) 1.0.4	Vega QSAR
BCF Model (Caesar) 2.1.14	Vega QSAR
BCF Model (Meylan) 1.0.3	Vega QSAR
BCF Model (KNN/Read-Across) 1.1.0	Vega QSAR
Persistence A54:A55	Vega QSAR
Persistence (Soil) Model (IRFMN) 1.0.0	Vega QSAR
Persistence A53:A55(Water) Model (IRFMN) 1.0.0	Vega QSAR
96-Hour Fathead Minnow 50 Percent Lethal Concentration (Lc50)	T.E.S.T.
48-Hour Daphnia Magna 50 Percent Lethal Concentration (Lc50)	T.E.S.T.
Tetrahymena Pyriformis 50 Percent Growth Inhibition Concentration (Igc50)	T.E.S.T.
Oral Rat 50 Percent Lethal Dose (Ld50) Exit	T.E.S.T.
Bioconcentration Factor (BCF)	T.E.S.T.
Developmental Toxicity (DEVTOX) Exit	T.E.S.T.
Ames Mutagenicity (Mutagenicity	T.E.S.T.
Normal Boiling Point	T.E.S.T.
Flash Point	T.E.S.T.
Surface Tension @25	T.E.S.T.
Viscosity @25c	T.E.S.T.
Density	T.E.S.T.
Water Solubility @25c	T.E.S.T.
Thermal Conductivity @25c	T.E.S.T.
Vapor Pressure @25c	T.E.S.T.
Melting Point	T.E.S.T.
Bioconcentration Factor (BCF)	Epi-Suite
Persistence (Soil)	Epi-Suite
Persistence (Water)	Epi-Suite
Persistence (Air)	Epi-Suite

Persistence (Silt)	Epi-Suite

Appendix 4: OPFR Full Data Tables

Hazard Score/ Endpoint	*AT*	*C*	*R*	*D*	*M*	*E*	*AA*	*P*	*B*	*Averages*
vL	0	0	0	0	0	0	0	0	33	3.777778
L	36	20	9	9	41	13	11	15	16	18.77778
M	28	30	41	56	29	29	11	22	9	28.33333
H	8	13	6	6	7	12	32	19	10	12.55556
vH	7	0	0	0	0	0	21	20	9	6.33333
DGap	18	34	41	26	20	43	22	21	20	27.22222
Total	97	97	97	97	97	97	97	97	97	/
Data Source/Endpoint	*AT*	*C*	*R*	*D*	*M*	*E*	*AA*	*P*	*B*	*Averages*
Empirical	32	5	16	20	28	5	13	1	11	14.55556
Predicted	25	38	28	40	38	35	44	55	51	39.33333
Auth. So.	22	20	12	11	11	14	18	20	15	15.88889
DGap	18	34	41	26	20	43	22	21	20	27.22222
Total	97	97	97	97	97	97	97	97	97	/

Appendix 5: Wilcox Test and Bonferroni's Test α=0.05

Endpoint	P-Value	Bonferroni's Corrected	Significant Difference?
AT	0.833	1	No
C	0.8551	1	No
R	0.8551	1	No
D	1	1	No
M	1	1	No
E	0.8539	1	No
AA	1	1	No
P	0.5896	1	No
B	1	1	No

Appendix 6: OPFR Qualitative Data:
The following link will take you to an excel file for the full QCAT© data assessed.

https://drive.google.com/open?id=1yAUHwjl3ku7N0AXZHwELAc2H9YxTNNnI