Prioritizing hazardous chemicals in children's consumer products to improve health and safety

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Abstract

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This dissertation focuses on developing frameworks and supporting evidence for the prioritization of chemicals found in children's consumer products. Toxic chemicals found in children's consumer products can impact child health and development. In response to these concerns, Washington and other states have enacted laws requiring manufacturers to report the presence of toxic chemicals in children's consumer products. These laws have generated extensive data on the types of chemicals children might be exposed to in consumer products and can be useful sources of data for prioritizing chemicals for future action. This dissertation uses data from required reporting laws to generate a prioritization framework, characterize the accuracy of required reporting laws and hypothesize about the safety of alternatives to toxic chemicals. The first objective is to integrate the concentration of potentially hazardous chemicals found in children's products with exposure and toxicity data to develop a framework for prioritizing chemicals for future research and regulatory actions. We found that chemicals with high toxicity that are found in children's products with high potential for exposure, such as some phthalates, were among the highest priority chemicals. The second objective compares the concentrations of chemicals in children's products reported by manufacturers with independent assessments. We found that concentrations of toxic chemicals were generally higher in manufacturer reports than in measurements by the state. This may seem surprising,

but actually reflects the structure of the regulation which disincentives underreporting but is silent on overreporting. The final objective looks to the future by assessing the safety of alternative chemicals found in children's products by determining toxicities of both chemicals and alternatives using authoritative lists, in vivo data and in vitro data. Alternative chemicals were less likely to be considered endocrine disruptors by authoritative lists, however in vitro data revealed biological responses similar to the chemicals they are replacing. This suggests that in some cases, alternatives may not be safer, just less well characterized. Taken together, the objectives of this dissertation demonstrate the utility and importance of required reporting frameworks and point to modifications that can enhance reporting accuracy.

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Dissertation Introduction:

Children are uniquely susceptible to the myriad of environmental toxicants they are exposed to throughout development [1], many of which have not been fully evaluated for developmental, neurological, and other toxicities [2]. Consumer products represent an important exposure source for many toxicants due to their intended uses which lead to direct contact with children [2-6]. Examples of chemicals found in children's products include reports of phthalates in baby bottles [4], and brominated flame-retardants and lead in toys [5, 7]. In addition to the extensive array of chemicals found in children's products, the unique ways in which children interact with their environments and their increased biological susceptibility contribute to concerns about potential health impacts. Hand-to-mouth behavior is common among young children and increases the time a product may be in a child's mouth, consequently, increasing oral exposure potential [8]. Children also spend more time on or near the floor [8], increasing exposure to inhaled or ingested house dust, which can act as a reservoir for chemicals often derived from consumer products [9, 10]. Furthermore, because of their small body size, the dose associated with these exposures is proportionately greater than the dose adults receive [8].

In addition to higher potential exposure, children also lack fully developed organ systems and detoxification pathways, greatly increasing their biological susceptibility to toxicants. Examples of this increased susceptibility include the adverse neurodevelopmental impacts of early life exposure to lead [11] and mercury [12]. It is estimated the 5-20% of neurobehavioral disorders are attributable to environmental chemical exposures [13]. Many of the effects of developmental exposure to toxicants can persist throughout the lifetime, limiting children's abilities to reach their full potential. This has significant health and economic impacts. As of 2002, the United States' annual cost for environmentally attributable neurobehavioral disorders was $9.2 billion[13]. When four categories of disease (asthma, lead poisoning, neurobehavioral and cancer) with varying degrees of environmental attributability were considered, the total costs were equivalent with 2.8% of United States healthcare spending [13]. Because of the vast amounts of chemicals found in consumer products, regulatory agencies must prioritize some chemicals for action. In order for the EPA and State governments to make timely and informed decisions about children's chemical safety and sustainability, it is important to integrate current toxicity and exposure sciences databases in a child-specific manner that can be used to prioritize chemicals for further research and regulation.

In the United States, the Consumer Product Safety Improvement Act of 2008 limits the use of some hazardous chemicals, including six phthalates, lead and cadmium in children's products [14]. Lead is not permitted in children's products in concentrations greater than 100 ppm for total lead and 90 ppm for surface coatings. Diethyl hexyl phthalate, dibutyl phthalate, butyl benzyl phthalate, diisononyl phthalate, di-n-pentyl phthalate, di-n-hexyl phthalate (DHEXP), dicyclohexyl phthalate and diisobutyl phthalate are restricted to no more than 1000 ppm per individual phthalate in children's toys and product designed to care for children under age three. Diisononyl phthalate, diisodecyl phthalate and di-n-octyl phthalate are restricted in concentrations greater than 1000 ppm per individual phthalate in children's toys that can be placed in a child's mouth and in products designed for care of children under age three. While these laws help improve product safety, the permissible limits per phthalate are still relatively high and products may contain multiple restricted phthalates. Additionally, the Consumer Product Safety Improvement Act narrowly defines children's products, excluding clothing,

footwear and cosmetics. These factors have limited the Act's effectiveness in protecting children.

In response to potentially toxic chemicals found in consumer products, WA Department of Ecology (Ecology) implemented The Children's Safe Product Act (CSPA), requiring that children's products manufacturers report the concentration range of 85 chemicals of high concern in children's products sold in WA [15]. The CSPA database contained over 44,000 records in January 2017. Manufacturers are required to the concentration range, product description, intended age for product use, chemical functional use, date and manufacturer for any product that contains greater than 100ppm of any of the 85 chemicals of high concern to children. Three of the primary limitations of this structure are that manufacturers do not report products that tested negative for chemicals of high concern to children, manufacturers do not report a method or level of detection for the chemical and lastly concentrations are reported in ranges, leading to uncertainty. Ecology also maintains a product-testing database with results from independent analyses of consumer products that contains specific concentrations, laboratory methods and the level of detection [16]. The product-testing database is a unique resource. As more states are adopting regulatory frameworks similar to CSPA, none have reported a publicly available independent database of product testing results. Because these resources were designed for enforcement purposes, they have not been incorporated into new Public Health assessments and decisions.

One goal of CSPA is to prioritize chemicals for future action. In order to do this, regulators must be able to consider factors related to the product and the hazardous chemical. In order to identify the high priority chemical/product combinations using the complex and multilayered CSPA database we need a framework that considers the lifestage-specific toxicity of the chemical, exposure range and potential dose and product use. This dissertation builds a framework that allows for prioritization of unique product-chemical reports under the CSPA database. This tool can be used as a primary screening method to help regulatory agencies sift through thousands of records in a relatively short time.

Despite the complexity and extensiveness of the CSPA database, there are some limitations due to uncertainty of precise chemical concentrations, levels of detection and analytical methods. Ecology's product testing database provides details regarding the analytical methods, level of detection, product component and purchase date. Results from Ecology's product testing database provide have the ability to provide a "gold standard" for comparison to the manufacturers reported CSPA results. Because this resource is primarily used to enforce regulations on total concentrations of phthalates and some metals in children's product, to date, a wide-scale comparison of the correlations between the two databases has not been conducted. Knowing the degree of alignment between manufacturers reported data and Ecology's independent analyses would help characterize the degree of uncertainty surrounding the CSPA data. In this dissertation, we conduct a product and chemical specific comparison of the product-testing database and the CSPA data. The results provide insight to the necessity of maintain an active product testing laboratory to reduce uncertainty regarding concentrations of chemicals in consumer products and determine whether the reporting concentration ranges under CSPA are appropriate for addressing and reducing public health impacts. Understanding the relationships between the product testing database, the CSPA database and public health impacts, helps us learn to make better decisions and take more effective actions to prevent children's exposure to toxic chemicals in consumer products.

However, removing toxic chemicals from children's products only protects public health when they are replaced with safer alternatives. The principles of green chemistry aim to develop safer chemicals by reducing and eliminating the use of hazardous substances by considering potential health and ecological hazards from creation through disposal [17]. Safer chemical substitutions are often identified by alternatives assessments. Guidance documents for alternatives assessments have been released by the National Academy of Sciences, Interstate Chemical Clearinghouse[18], the Environmental Protection Agency[19] and the Office for Economic Cooperative Development [20]. The National Academy of Sciences (NAS) specifically focused on the selection of alternative chemicals [21]. Because alternatives analysis requires the full hazard assessment of at least two chemicals, data gaps are likely to exist, especially for newer chemicals. Lack of data is not an indication of safety and approaches to bridge data gaps are highly important for alternatives assessments.

Bisphenol A (BPA) is used as a coating for plastic consumer products, such as water bottles, food storage containers and electronics. While BPA has not been banned in the United States, the Food and Drug Administration (FDA) has restricted BPA concentrations in baby bottles, sippy cups and some food packaging due to its endocrine disrupting capability and reproductive and developmental toxicity [22]. While initial studies of the effects of BPA in humans had mixed results, the contribution of more recent studies have supported the hypothesis that BPA can have low-dose effects that are different from higher dose impacts. Low dose exposures can be particularly damaging during sensitive periods of development [23]. Despite the lack of more extensive regulation from the Consumer Product Safety Commission and the FDA, consumer concern has driven the development of BPA-free products. Many of these products contain bisphenol-S (BPS) as a replacement compound. While some assessments have found BPS to be safe in children's products [24], others find that BPS has similar toxicological attributes as BPA [25, 26].

Phthalates, bisphenols and parabens are examples of chemicals groups that are being either voluntarily or legally phased-out of children's products. Phthalate and paraben free products pepper grocery stores, pharmacies and other retailers. Identification of replacement chemicals and comparisons of toxicity using both existing consensus reports and in vitro toxicity screening will allow us to make predictions about whether BPA, phthalate or paraben-free products are improvements for public health. This dissertation contains a case study of phthalate, BPA, parabens and their alternatives to determine whether predictive toxicology tools and high throughput screening methodologies can improve data availability for conventional and alternative chemicals.

The overall goal of this dissertation is to fill the research needs related to translating the CSPA and product testing results from databases to public health action. This goal is addressed in the subsequent three chapters:

Chapter 1: Develop a framework for prioritizing CSPA data by considering exposure and toxicity

Hypothesis 1A: A mathematical framework for the integration of lifestage, exposure factors, toxicity and potency will allow for the prioritization of chemicals and products in the CSPA database.

Chapter 2: Determine whether there are differences in the chemical concentrations reported in the CSA manufacturers' database and the product testing database and whether these differences impact chemical prioritization in children's products

Hypothesis 2A: There will be a significant correlation between chemical concentrations reported from the CSPA manufactures' database and the product-testing database.

Chapter 3: Determine whether in vitro data can improve chemical prioritization for alternative chemicals

Hypothesis 3A: Replacement chemicals will be less well characterized by existing databases, such as IARC and the EU existing substances database.

Hypothesis 3B: Replacement chemicals will have in vitro activity, as assessed by ToxCast assays, similar to the chemicals they are replacing.

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CHAPTER 1:

Title: A Toxicological Framework for the Prioritization of Children's Safe Product Act Data

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Abstract: In response to concerns over hazardous chemicals in children's products, Washington State passed the Children's Safe Product Act (CSPA). CSPA requires manufacturers to report the concentration of 66 chemicals in children's products. We describe a framework for the toxicological prioritization of the ten chemical groups most frequently reported under CSPA. The framework scores lifestage, exposure duration, primary, secondary and tertiary exposure routes, toxicokinetics and chemical properties to calculate an exposure score. Four toxicological endpoints were assessed based on curated national and international databases: reproductive and developmental toxicity, endocrine disruption, neurotoxicity and carcinogenicity. A total priority index was calculated from the product of the toxicity and exposure scores. The three highest priority chemicals were formaldehyde, dibutyl phthalate and styrene. Elements of the framework were compared to existing prioritization tools, such as the United States Environmental Protection Agency's (EPA) ExpoCast and Toxicological Prioritization Index (ToxPi). The CSPA framework allowed us to examine toxicity and exposure pathways in a lifestage-specific manner, providing a relatively high throughput approach to prioritizing hazardous chemicals found in children's products.

Key Words: Chemical Prioritization, ToxCast, ExpoCast, Consumer Products, Children's Health

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1. Introduction

Children are uniquely susceptible to the myriad of environmental toxicants they are exposed to throughout development [1], many of which have not been fully evaluated for developmental, neurological, and other toxicities [2]. Consumer products represent an important exposure source for many toxicants due to their intended uses which lead to direct contact with children [2-6]. Examples of chemicals found in children's products include reports of phthalates in baby bottles [4], and brominated flame-retardants and lead in toys [5, 7]. In addition to the extensive array of chemicals found in children's products, the unique ways in which children interact with their environments and their increased biological susceptibility contribute to concerns about potential health impacts. Hand-to-mouth behavior is common among young children and increases the time a product may be in a child's mouth, consequently, increasing oral exposure potential [8]. Children also spend more time on or near the floor [8], increasing exposure to inhaled or ingested house dust, which can act as a reservoir for chemicals often derived from consumer products [9, 10]. Furthermore, because of their small body size, the dose associated with these exposures is proportionately greater than the dose adults receive [8].

In addition to higher potential exposure, children also lack fully developed organ systems and detoxification pathways, greatly increasing their biological susceptibility to toxicants. Examples of this increased susceptibility include the adverse neurodevelopmental impacts of early life exposure to lead [11] and mercury [12]. It is estimated the 5-20% of neurobehavioral disorders are attributable to environmental chemical exposures [13]. Many of the effects of developmental exposure to toxicants can persist throughout the lifetime, limiting children's abilities to reach their full potential. This has significant health and economic impacts. As of 2002, the United States' annual cost for environmentally attributable neurobehavioral disorders was $9.2 billion[13].

In the United States, the Consumer Product Safety Improvement Act of 2008 limits the use of some hazardous chemicals, including six phthalates, lead and cadmium in children's products. Lead is not permitted in children's products in concentrations greater than 100 ppm for total lead and 90 ppm for surface coatings. Three phthalates; diethyl hexyl phthalate, dibutyl phthalate and butyl benzyl phthalate concentrations are restricted to no more than 1000 ppm per individual phthalate in children's toys and product designed to care for children under age three. Diisononyl phthalate, diisodecyl phthalate and di-n-octyl phthalate are restricted in concentrations greater than 1000 ppm per individual phthalate in children's toys that can be placed in a child's mouth and in products designed for care of children under age three. While these laws help improve product safety, the permissible limits per phthalate are still relatively high and products may contain multiple restricted phthalates. Additionally, the Consumer Product Safety Improvement Act narrowly defines children's products, excluding clothing, footwear and cosmetics. These factors have limited the Act's effectiveness in protecting children.

In response to concerns over children's exposure to hazardous chemicals found in consumer products, Washington State's Department of Ecology (Ecology) implemented the Children's Safe Product Act (CSPA). Enacted shortly before the Consumer Product Safety Improvement Act of 2008, CSPA imposes more stringent regulatory limits on the concentrations of lead, cadmium and phthalates in children's products sold in Washington State. Under CSPA total phthalate concentration in children's products must be under 1000 ppm. Additionally, CSPA requires that

children's product manufacturers report the concentration range for 66 chemicals of high concern to children in any child's product sold or manufactured in Washington State (66 chemicals were on the list at the time of this work and by 2019 this number expanded to 85 chemicals). Chemicals reported under CSPA were selected based on toxicity and potential for children's exposure. Ecology established the 66 chemicals for required reporting based on a multi-phase prioritization process that highlighted carcinogenicity, reproductive & developmental toxicity, and endocrine disruption as toxicity endpoints [27]. Phthalate and cadmium concentrations are reported under CSPA; however, because lead is tightly regulated at the federal level, it was not included as a chemical of concern under CSPA's mandatory reporting requirement.

As of September, 2015 there were over 33,000 reports in the CSPA database [15]. Products reported include toys, children's cosmetics, children's jewelry, children's clothing, child car seats and other products related to child care. Within the CSPA database, products are classified in a hierarchical system with 'segment' being the broadest and 'brick' being the narrowest category. Segment examples include arts and crafts, baby care, beauty/ personal care and clothing. Chemical concentrations are reported to fit within one of six ranges (<100, 100-500, 500-1000, 1000-5000, 5000-10,000 and >10,000 ppm). Along the concentration range, manufacturers report the function of the chemical in each product from a list including, coloration, pigments and dyes, surfactant, plasticizers and even chemicals found in the product that serve no function and are contaminants. Manufacturers also report whether the product is designed for a child under age three, or age three and above. This information is useful for characterizing how children's exposures to these products may occur and in what capacity.

However, interpreting the complex, multilayered CSPA database requires an innovative framework that considers the lifestage-specific toxicity of the chemical and potential exposure routes. We have constructed a framework for the incorporation of these important factors into the toxicological prioritization of the CSPA data. The goals of this paper are to develop a framework for the prioritization and identification of high priority chemicals reported under CSPA and compare the results to other prioritization tools, such as the United States Environmental Protection Agency's (EPA) ExpoCast and Toxicological Priority Index (ToxPi) and make recommendations to improve the collection of data relevant for prioritizing action on children's products. The results of this work will help focus further efforts to protect children from potentially harmful chemicals found in consumer products.

2. Methods

2.1 Chemicals Considered: This framework was developed from the reports available from August, 2012-September, 2015, a total of 33,000 entries [15]. CSPA reports by chemical are shown in supplemental table S1. The ten most frequently reported chemical groups included cobalt and cobalt compounds, ethylene glycol, phthalates, methyl ethyl ketone, antimony, octamethylcyclotetrasiloxane, styrene, formaldehyde, molybdenum, and parabens. Reports for the 10 most frequently reported chemical groups covered approximately 88% of the 33,000 records in the CSPA database. Because the chemical properties and toxicities vary between phthalates and parabens, these chemical groups were disaggregated into individual chemicals for framework development. The metal groups could not be disaggregated into specific metalloid compounds since only total metal mass is reported.

2.2 Framework Development: The framework for the toxicological interpretation of the CSPA data assigns scores to attributes of each product reported in the database and then integrates the scores to identify chemicals of higher concern based on both toxicity and exposure potential. Product and chemical attributes are scored on a zero to three scale: lifestage, exposure duration, chemical concentration, chemical properties, toxicokinetics, and systemic toxicity endpoints and potency. Variables with one or fewer priority points are of less concern while those with three present the most urgent concern. Products (1) designed for children under the age of three (2) intended for long-term exposure that have (3) high concentrations of (4) chemicals of high toxicity that are (5) likely to be absorbed orally, dermally or through inhalation get the most priority points. Variable scores are described in detail below. The rationale and relevant references for score assignment are shown in Table 1 and the scores for each chemical are shown in Table 2.

2.3 Framework Equations: The framework uses an equally weighted multi-attribute utility function to calculate the total priority index from an exposure score and a toxicity score. Numeric scores are shown in Tables 1 and 2.

The framework is composed of three components; the exposure score, the toxicity score and the total priority index. The exposure score is a calculation based on attributes of the product and chemical that increase the likelihood of child exposure (equation 1). The toxicity score is a combination of endpoint certainty and potency scores (equation 2). The product of the exposure score and toxicity score is the total priority index (equation 3). Equation 4 calculates an endocrine disruptor score that can be compared with other prioritization schemes.

The exposure score is the sum of the individual product variables: lifestage, exposure duration, applicability and concentration added to the sum of the products of the exposure route likelihood and exposure route absorption for oral, dermal and inhalation exposures. The exposure route absorption score is the average of the score for measured absorption and the score for predicted absorption based on chemical properties. Because measured absorption scores were not available for all chemicals, averaging chemical property scores and measured absorption scores minimized bias induced by lack of data. The exposure absorption score is multiplied by the exposure route likelihood. This means that products likely to have, for example, high oral exposures, such as pacifiers, with chemicals that are highly absorbed through the oral route will have high exposure scores relative to products with chemicals less likely to be absorbed through the expected exposure route.

Equation 1:
Exposure Score:
$(LS+EX+A+Con)*[(O_{MF}(S+Abs_{oral})/2)+(I_{MF}(VP+Abs_{inhalation})/2)+(D_{MF}(K_p+Abs_{dermal})/2]$

Where LS is the lifestage score, EX is the exposure duration score A is the applicability score, Con is the concentration score, O_{MF} is the oral exposure route modifying factor, S is water solubility score, Abs_{oral} is the oral absorption score, I_{MF} is the inhalation exposure route modifying factor, VP is vapor pressure score, $Abs_{inhalation}$, D_{MF} is the dermal exposure route modifying factor, K_p is the dermal permeability constant score and Abs_{dermal} is the dermal absorption score.

The toxicity score is the sum of the products of the certainty and potency scores for endocrine disruption, reproductive and developmental toxicity, carcinogenicity and neurotoxicity. The

certainty score reflects the overall confidence of international and national databases in whether the chemical causes the specific toxicity endpoint. This is multiplied by the potency to ensure that known toxicants that are highly potent will have higher toxicity scores.

Equation2:

Toxicity Score: ($ED_{certainty}$*$ED_{potency}$)+ ($RD_{certainty}$*$RD_{potency}$)+ ($C_{certainty}$*$C_{potency}$) +($NT_{certainty}$*$NT_{potency}$)

Where ED is endocrine disruption, RD is reproductive and developmental toxicity, C is carcinogenicity and NT is neurotoxicity

The total priority index is calculated by the product of the exposure score and toxicity score. This score is unique to each report (product and chemical specific) in the CSPA database.

Equation 3:

Total Priority Index: Exposure Score*Toxicity Score

The endocrine disruptor score is a modification of the total priority index that is specific to endocrine disruption. It is the product of the exposure score, endocrine disruption certainty score and endocrine disruption potency score. Similar scores can be calculated for reproductive and developmental toxicity, carcinogenicity and neurotoxicity. Endocrine disruption is highlighted in this example because it can be compared to other prioritization frameworks.

Equation 4:

Endocrine Disruptor Score: Exposure Score* $ED_{certainty}$*$ED_{potency}$

Where $ED_{certainty}$ is the certainty score for endocrine disruption and $ED_{potency}$ is the potency modifying factor for endocrine disruption

2.4 Equation Variables: All variables are described in Table 1 and in detail below.

Table 1: Equation variables and basis for calculating the scores. Variables were assigned a score on a 0-3 scale based on reported data in CSPA (lifestage, concentration, exposure duration, exposure routes) or chemical factors (chemical properties, toxicokinetics, toxicity and potency).

Variable	Equation Abbrev.	Score			Basis	Mathematical Role
		1	2	3		
Lifestage	LS	Ages 3 -12		Under 3	As reported in target age[15]	Additive to calculate product exposure potential
Concentration (ppm)*	Con	100-500*	1000-5000*	10,000+*	As reported concentration [15]	
Exposure duration	EX	Short-term		Long-term	As reported in product segment [15]	
Applied directly to skin	A	No		Yes	As Reported in product segment[15]	

Oral exposure	O_{MF}	Tertiary	Secondary	Primary	Product segment (primary), Target age (secondary)[15]	Modifying factor for toxicokinetics for oral exposure
Water solubility (moles/L)	S	<0.001	0.001-0.01	>0.1	Soluble (3), moderately soluble (2), insoluble (1) [28]	Averages with Abs_{oral} for oral exposure toxicokinetics
Oral absorption	Abs_{oral}	1-5%	Absorbed at unknown rate	Above 5%	Absorption rate through oral exposure (ATSDR) [29]	Averages with solubility for oral exposure toxicokinetics
Dermal exposure	D_{MF}	Tertiary	Secondary	Primary	As reported product segment (primary) [15]	Modifying factor for toxicokinetics for dermal exposure
Dermal permeability constant	K_p	<3.39E-03	3.4E-03-6.67E-03	>6.7E-03	Based on the tertiles of the Kp[30, 31]	Averages with Abs_{dermal} for dermal exposure toxicokinetics
Dermal exposure absorption	Abs_{dermal}	1-5%	Absorbed at unknown rate	Above 5%	Absorption rate through dermal exposure (ATSDR)[29]	Averages with K_p for dermal exposure toxicokinetics
Inhalation exposure	I_{MF}	Tertiary	Secondary	Primary	As reported product segment[15]	Modifying factor for toxicokinetic for inhalation exposure
Vapor Pressure mmHg at 25 degrees C	VP	<0.075 mmHg	0.075-32mmHg	> 32 mmHg	VP ranges for volatile compounds (3), semi-volatile compounds (2) and nonvolatile compounds (1)	Averages with $Abs_{inhalation}$ for inhalation exposure toxicokinetics
Inhalation exposure absorption	$Abs_{inhalation}$	1-5%	Absorbed at unknown rate	Above 5%	Absorption rate through inhalation exposure (ATSDR)[29]	Averages with VP for inhalation exposure toxicokinetics
Reproductive and	$RD_{certainty}$	Potential RD^	Suspected RD^	Known RD	ECHA Existing Substances[32]	Multiplies with $RD_{potency}$

developmental toxicity certainty#					, Prop 65[33], Global Harmonization Standard[34]	
Reproductive and developmental potency	$RD_{potency}$	NOAEL >397 mg/kg	NOAEL 200-297 mg/kg	NOAEL < 200 mg/kg	NOAEL from ECHA Existing Substances[32]	Modifying factor $RD_{certainty}$
Carcinogenicity certainty#	$C_{certianty}$	Potential Carcinogen ^	Suspected Carcinogen ^	Known Carcinogen ^	IARC[35], Prop 65[33], Global Harmonization Standard[34], EPA IRIS[36]	Multiplies with $C_{potency}$
Carcinogenicity potency	$C_{potency}$	TD50 >465 mg/kg	TD50 from 233- 465 mg/kg	TD50 <233 mg/kg	Dose that causes a tumor in 50% of the study population (TD50) from the Carcinogenic Potency Database[37, 38]	Modifying factor for $C_{certainty}$
Endocrine disruption certainty#	$ED_{certianty}$	Potential ED^	Suspected ED^	Known ED	ECHA Endocrine Disruptor Substances of Concern[39], Global Harmonization Standard[34]	Multiplies with $ED_{potency}$
Endocrine disruptor potency	$ED_{potency}$	NOAEL >336 mg/kg	NOAEL 336-667 mg/kg	NOAEL >667mg/kg	LOAEL from ECHA Endocrine Disruptor Substances of Concern[39]	Modifying factor for $ED_{certainty}$
Neurotoxicity certainty #	$NT_{certainty}$			Known NT	Grandjean and Landrigan et al. 2014[40] , Global Harmonization Standard[34]	Multiplies with $NT_{potency}$
Neurotoxicity potency	$NT_{potency}$		All NTs		Because potency data is not available, all known neurotransmitt	Modifying factor for $NT_{certainty}$

					ers re assigned a score of 2.	

*For chemical concentrations under 100ppm a score of 0.5 was assigned, for chemical concentrations between 500 and 1000ppm a score of 1.5 was assigned and for chemical concentrations between 5000 and 10,000ppm a score of 2.5 was assigned. # Chemicals not considered toxic for the endpoints specified in the resources consulted for this study received a certainty score of 0. ^Chemicals with potential and suspected toxicities did not have associated potency data and received a potency score (modifier) of 1.

2.4.1 Lifestage: When manufacturers report data to the CSPA database, they are required to state whether the product is designed for a child under age three or age three to 12. Children under the age of three have unique susceptibility factors that may make them more vulnerable to toxic chemical exposures as well as increased hand-to-mouth behavior. Products designed for children under age three are assigned lifestage score of three and products for children over age 3 are assigned a lifestage score of one (Table 1 and 2).

243.2 Chemical Concentration: Manufacturers are required to include the concentration range of the chemical when reporting to the CSPA database. There are six chemical concentration ranges (shown in Table 1) that were scored on 0.5 increments from 0.5 to 3.

2.4.3 Exposure Routes: Exposure routes were assigned scores based on whether the relevant route, for example, dermal, is likely to be a primary, secondary or tertiary exposure route. When manufacturers report to the CSPA database, they must also include a product description from a finite list of product segment and brick levels. The primary exposure route was determined by the product segment description. For the categories of clothing, beauty/personal hygiene, footwear, arts and crafts, household, and camping the primary exposure route was considered to be dermal. For kitchen merchandise the primary exposure route was considered to be oral. Fragrances and party blowers were assigned two primary exposures because fragrances are applied to the skin, but also inhaled and because party blowers are inserted into the mouth and blown through. Baby care products were assessed by the product brick description and those that involved feeding support, pacifiers or food preparation were considered to have primary oral exposures. Toys and games were considered to have primarily dermal exposures with the exception of kitchen toys, these were considered to have oral exposures. Products with primary oral exposure were assigned secondary dermal exposures because children usually hold toys that they put in their mouths. Paints were determined to have primary inhalation, secondary dermal and tertiary oral exposures. If the product was intended for a child under the age of three and the primary route was not oral, then the secondary route was oral. For records without oral or inhalation as primary or secondary exposures, two tertiary exposures of oral and inhalation were assigned. This is to account for the fact that products may disintegrate overtime and accumulate in house dust which children inhale and ingest. Children may inhale chemicals of concern through the vaporization of chemicals or through product disintegration. Primary exposure routes were assigned a modifying factor of three, secondary exposure routes were assigned a modifying factor of two and tertiary exposure routes were assigned a modifying factor of one (Tables 1 and 2). For example, a shirt for an infant may be associated with primary dermal exposures, but have secondary oral exposures as young children have frequent hand to mouth activities. For this example, the shirt would receive a score of three for dermal exposure

route and two for oral exposure route and one for inhalation exposure route. The exposure route score modifies the toxicokinetic score such that products with chemicals highly absorbed through a specific exposure route receive a higher score when that is the primary exposure route rather than when the route is secondary or tertiary.

2.4.4 Exposure Duration: The exposure duration score was determined by the Product Segment Description. For product segments including clothing, footwear, personal care/hygiene, and camping the exposure duration was assumed to be long-term. For product segments such as Toys/Games, Stationery/Office Machinery/Occasion Supplies, and Arts/Crafts/Needlework the exposure was assumed to be short-term. Short-term exposures were assigned a score of 1 and long-term exposures were assigned a score of 3 (Tables 1 and 2)

2.4.5 Applied Directly to Skin: Products in the personal hygiene product segment are intended for direct application to skin or body, such as lotions and cosmetics, and were therefore assigned a score of three. Those not designed for direct application to skin or body were scored as 1 (Tables 1 and 2).

2.4.6 Chemical Properties: The chemicals were scored based on properties that avail them to absorption through inhalation, oral or dermal exposures. The vapor pressure was used to assess potential for inhalation exposure. Vapor pressures under 0.075 mmHg at 25 C were assigned a score of one, as this vapor pressure is associated with nonvolatile chemicals. Chemicals with vapor pressures between 0.075and 32mmHg at 25 C were considered to have the potential inhalation exposures and were therefore assigned a score of 2. This vapor pressure range is associated with semi-volatile compounds. Chemicals with vapor pressures over 32 mmHg were assigned a score of three as this range reflects volatile organic chemicals.

Water solubility was used to assess the potential for oral exposure. Chemicals with lower water solubilities are less likely to be ingested through chewing/sucking on products. Chemicals considered generally insoluble (<0.001 mol/l) were assigned a score of 1. Chemicals with solubilities between 0.001 and 0.01 mol/l were assigned a score of 2 and chemicals considered soluble (>0.01mol/l) were assigned a score of 3 [28].

The skin permeability rate constant was calculated based on the water-octanol partitioning coefficient and the molecular weight as described in Potts and Guy, 1992, using the National Institute for Occupational Health and Safety's skin permeability calculator [30, 31]. Skin permeability constants (Kp) were assigned scores based on the distribution of those reported for this dataset. The lowest tertile scored one, the middle tertile scored two and the highest tertile scored three. Chemical property rationale and score are described in Tables 1 and 2.

2.4.7 Absorption: The percent of the chemical that is absorbed through inhalation, dermal or oral exposure was scored on a scale of one to three. For most chemicals, the Agency for Toxic Substances and Disease Registry (ATSDR) chemical profile included the percentage of chemical absorbed through oral, dermal and inhalation exposures. When available, this database was compiled using human data. Animal or in vitro data was used when human data was not available. If the absorption rate was between 1 and 5% the chemical scored 1. If the chemical was reported to be absorbed in humans but at an unknown rate, or if the chemical was absorbed between 5 and 10%, a score of two was assigned. If the absorption rate was above 10% a score of three was assigned. Absorption levels are shown in Tables 1 and 2.

2.4.8 Toxicity Endpoints: Endocrine disruption, reproductive and developmental toxicity, carcinogenicity and neurotoxicity were selected as relevant health endpoints. In order to remove potential biases, all of these endpoints were assessed based on curated databases. This approach builds on the initial selection process that identified the original 66 chemicals included in the CSPA database[13]. For each endpoint, chemicals were classified based on certainty of toxicity and potency. Scores for certainty and potency are shown in Table 1.

Endocrine disruption certainty was scored based on the European Chemicals Agency (ECHA) Endocrine Disruptor Substances of Concern database [39]. This list was created to prioritize chemicals for further review. Substances are categorized from 1-3. Category 1 includes known endocrine disruptors while categories 2 and 3 include suspected endocrine disruptors. In this scoring framework chemicals received a zero if they were not included in the list, a score of one if they were included on the candidate list, but not classified, a score of two if the ECHA assigned them to category 2 or 3 and a score of three if the ECHA assigned them to category 1.

Reproductive and developmental toxicity was assessed based on the Globally Harmonized System (GHS) of Classification and Labeling of Chemicals [34], the European Union's Existing Substances Regulation [32], and the Proposition 65 List [33]. The GHS classification system was created in 2001 and adopted by the United Nations in 2003 as a method for standardizing international information on toxic substances. The European Union's Existing Substances Regulation provides detailed risk assessment data for 141 chemicals. The Proposition 65 list is an updated list created by the California Office of Environmental Health Hazard Assessment that contains chemicals that are known or suspected carcinogens and reproductive toxicants [33]. Because none of these individual sources are comprehensive, a score was assigned based on the highest classification in any one of these sources. For example, if a chemical is classified as a known reproductive toxicant by proposition 65, but not included in the GHS or the EU existing substances regulation, then that chemical would be considered a known reproductive toxicant. Known reproductive toxicants received a score of three, suspected reproductive toxicants scored two, and those that are potentially reproductive toxicants scored one. Those with no data included received a zero.

Carcinogenicity was assessed based on IARC classification [35], The EPA's IRIS database[36], the GHS, and Proposition 65. Similar methods were used to assign carcinogenicity points: a score of three was assigned to known carcinogens, a score of two was assigned for suspected carcinogens, a score of one was assigned to potential carcinogens and chemicals not included in any of these sources received a zero.

Neurotoxicity was assessed based on Grandjean and Landrigan, 2014[40] and the GHS. If chemicals are listed as neurotoxicants in Grandjean and Landrigan, 2014, they received a score of three, if not they received a score of zero. Chemicals were also classified as neurotoxicants based on the GHS classification. Toxicity endpoint scores and rationale are shown in Tables 1 and 2.

2.4.9 Toxicity Potency: Estimating toxicity potency is a complex task that is highly dependent on the endpoints assessed and concentrations administered. Because of this, toxicity potency is assessed within each toxicity endpoint category (carcinogenesis, neurotoxicity, endocrine disruption and reproductive and developmental toxicity).

For endocrine disruption, the lowest observable adverse effect levels (LOAELs) and no observable adverse effects levels (NOAELs) recorded in the European Chemical Agency's Endocrine Disruptor Substances of Concern Database as of January 22, 2016, were used to calculate the potency. Endpoints included testis impacts (decreased sperm count, degeneration of spermatogenesis, changes in testis weight, leydig cell alterations) and sex hormone secretion impacts (Table S2). The NOAELs for reproductive and developmental toxicants from the European Chemical Agency's Existing Substances Database (as of January 22, 2016,) was used to calculate reproductive and developmental toxicity potency for most chemicals. NOAELs were derived from studies examining testis damage following in utero exposure, embryotoxicity, decreased offspring survival and fetal body weight (Table S2). The reproductive and developmental toxicity potency score for di-N-hexyl-phthalate was based on the LOAEL reported in the NTP monographs [41]. The potency score for reproductive and developmental toxicity for methyl ethyl ketone was based on a reference dose (RfD) reported in the US EPA's IRIS. The RfD was converted to a NOAEL by multiplying by the reported uncertainty factors. Supplemental Table S2 shows the NOAELs, LOAELS, RfDs and scores for potency for reproductive and developmental toxicity and endocrine disruption. An uncertainty factor of ten was used to convert LOAELs to NOAELs so that the critical doses could be compared across chemicals. For endocrine disruption and reproductive and developmental toxicity, potency scores were assigned a score of one to three based on the tertiles of the range of the NOAELs and LOAELs reported.

Carcinogenic potency was based on the dose that causes tumors in half the population (TD_{50}). This data was derived from the Carcinogen Potency Database [38]. For each known carcinogen, the TD_{50} for mice and rats was reported. The lower TD_{50} of the two species was used. TD_{50}s were scored based on the tertiles of the range reported.

For any endpoint categorized as a potential or suspected carcinogen, endocrine disruptor or reproductive and developmental toxicant, a potency score of one was assigned. In most cases, NOAELs and LOAELs are not available for potential and suspected toxicants. Because the potency is multiplied by the certainty score, a score of 1 for suspected and potential toxicants prevents the loss of consideration of the certainty score. For neurotoxicants, there was not a sufficient source of LOAELs or NOAELs for classification of potency. In order for the neurotoxicant effects to not be underweighted in the toxicity score, an artificial potency factor of three was used. Potency is shown in Tables 1 and 2.

Table 2: Scores assigned to each chemical based on the approach described in the text. Chemicals are sorted based on the highest total priority index. Rationale and criteria for the scores are shown in Table 1.

	Oral Absorption Score	Dermal Absorption Score	Inhalation Absorption Score	Water Solubility Score	Skin Permeability Constant Score	Vapor Pressure Score	RD Certainty Score	RD Potency Score	Carcinogenic Certainty Score	Carcinogen Potency Score	Neurotoxicity Certainty Score	Neurotoxicity potency Score	ED Certainty Score	ED Potency Score
Dibutyl phthalate	3	2	2	1	3	1	3	3	0	NA	3	2	3	3
Di-2-ethylhexyl phthalate	3	2	2	1	2	1	3	3	3	1	0	NA	3	3
Formaldehyde	2	3	3	3	1	3	1	1	3	3	3	2	0	NA
Butyl benzyl phthalate	3	2	3	1	3	1	3	3	0	NA	0	NA	3	3
Styrene	2	2	3	1	3	2	2	1	3	3	3	2	0	NA
Diisodecyl phthalate	3	NI	3	1	2	1	3	3	0	NA	0	NA	2	1
Methyl Ethyl Ketone	2	NI	3	3	2	3	3	1	0	NA	3	2	0	NA
Di-n-Hexyl phthalate	NI	3	NI	1	2	1	3	3	0	NA	0	NA	2	1
Butyl Paraben	NI	NI	NI	1	3	1	0	NA	0	NA	0	NA	3	3
Ethylene Glycol	2	1	3	3	1	2	2	1	0	NA	3	2	0	NA
Ethyl Paraben	NI	NI	NI	1	3	1	0	NA	0	NA	0	NA	3	1
Cobalt and Cobalt Compounds	3	1	3	1	1	1	1	1	3	3	0	NA	0	NA
Diethyl phthalate	2	1	NI	1	2	1	0	NA	1	1	0	NA	3	3
Antimony and Antimony Compounds	2	2	2	1		1	0	NA	3	1	0	NA	0	NA
Diisononyl phthalate	3	1	3	1	2	1	1	1	0	NA	0	NA	2	1
Di-n-octyl phthalate	2	NI	NI	1	2	1	1	NA	0	NA	0	NA	1	1
Octamethylcyclotetrasiloxane	NI	NI	NI	1	3	3	1	1	0	NA	0	NA	0	NA
Methyl Paraben	NI	NI	NI	2	2	1	0	NA	0	NA	0	NA	0	NA
Molybdenum and Molybdenum Compounds	NI	NI	NI	1	1	1	0	NA	0	NA	0	NA	0	NA
Phthalic anhydride	NI	NI	NI	2	1	1	0	NA	0	NA	0	NA	0	NA
Propyl paraben	NI	NI	NI	1	3	1	0	NA	0	NA	0	NA	0	NA

RD is for reproductive and developmental, ED is for endocrine disruption, NI is for no information and NA is for not applicable. Potency scores were not applicable to chemicals without certainty scores.

2.5 Framework Assumptions:

1.) August 2012- September 2015 data is representative of the CSPA data as a whole, once phase in is complete in 2018
2.) Products intended for children under age three have the potential for oral exposure
3.) All products will disintegrate over time and the chemicals found in these products will accumulate in house dust leading to oral and inhalation exposure
4.) Exposures occur only through oral, dermal and inhalation exposure

2.6 Missing Data: In examples where data was available on toxicity endpoints, but not on exposure route absorption, the chemical properties alone were used to estimate potential for each exposure route. For some chemicals, such as molybdenum, methyl paraben, phthalic anhydride and propyl paraben, no data on toxicity endpoints were found in the databases consulted. For these chemicals, it is possible to use the exposure score to understand how they could enter children's bodies. The lack of toxicity score does not mean these chemicals are safe or unsafe, rather, based on existing data, it is not possible to assign priority points at this time.

2.7 Expocast: The US EPA developed ExpoCast as a high throughput system to screen and classify chemicals based on human exposure potential [42, 43]. The system is based on far-field mass balance human exposure models and has been shown to correlate with the National Health and Nutrition Examination Survey (NHANES) biomonitoring levels, especially for chemicals found in consumer products[42]. In this study, ExpoCast was accessed through the Interactive Chemical Safety for Sustainability Dashboard in January of 2016 to obtain median exposure predictions for chemicals reported under CSPA. ExpoCast estimates exposure predictions at the population level to almost 8,000 compounds[43]. Median predicted exposures in mg/kg/day were available for all CSPA chemicals except formaldehyde. For metals reported in CSPA as groups, all metalloid compounds available in ExpoCast were included.

2.8 ToxPi: The Toxicological Priority Index (ToxPi) considers the results from 85 in vitro ToxCast assays for potential estrogen, androgen and thyroid disruption as well as chemical properties to prioritize endocrine disruptors[44]. Filer et al. 2014 report ToxPi scores for 1858 chemicals available in phase II of ToxCast [45]. In addition to the original sources of endocrine disruption considered in Reif et al., 2013, Filer et al., 2014, also considered assays for glucocorticoid disruption PPAR activation [45] for a total of 85 in vitro assays. The assay results are also compared to 27 ToxCast assays for cytotoxicity to weed out any compounds that may be causing overt cellular toxicity. Of the CSPA chemicals used to develop this framework, 14 also had ToxPi scores. ToxPi scores were accessed via the supplemental material of Filer et al. 2014 [45] and compared to the endocrine disruption score in the CSPA database calculated in equation 4.

2.9 Statistical Software: The framework was constructed and analyzed using Microsoft Excel version 14.5.8. Scatterplots were made using R Studio version 0.99.491. A principal component analysis was conducted using JMP version 12.2.0 from the SAS Institute.

3. Results

The average exposure score across all chemicals was 10.4 with a standard deviation of 2.6 (Table 3). The three highest scoring chemicals for exposure were formaldehyde (average 14.2), octamethylcyclotetrasiloxane (average 13.9) and styrene (average 13.6). These three

chemicals' exposure scores were roughly average for most product characteristics, including lifestage, exposure duration, application to skin or body, and concentration. However, toxicokinetic scores, based on chemical properties and observed absorption rates were above average for all three chemicals for at least one exposure route. Across all records in the CSPA database, the maximum exposure score was 20.5 for formaldehyde in party horns and the minimum exposure score was 5 for molybdenum in drawing supplies. Toxicity scores were calculated by the sum of the products of the individual endpoint toxicities and potencies. The highest toxicity scores were for dibutyl phthalate (24), DEHP (21) and formaldehyde (21). Four chemicals, phthalic anhydride, propyl paraben, methyl paraben and molybdenum, were not listed as endocrine disruptors, neurotoxicants, reproductive toxicants or carcinogens in any of the databases used in this study.

Table 3: Exposure scores and total priority indices for the CSPA chemicals considered in this framework. Chemicals are sorted based on total priority index. The three chemicals with the highest exposure scores are highlighted in gray. Standard deviations (SD) represent the variability in scores or indices within each chemical or chemical group.

Chemicals	Number of Reports	Exposure Score +/- SD	Total Priority Index +/- SD
Formaldehyde	533	14.2+/-3.3	297.8+/-69.1
Dibutyl phthalate	778	12.3+/-1.7	294.7+/-40.1
Styrene	2251	13.6+/-2.7	231.2+/-45.1
Butyl benzyl phthalate (BBP)	610	12.5+/-1.7	225.2+/-30.2
Di-2-ethylhexyl phthalate	909	10.6+/-1.7	223.2+/-34.6
Diisodecyl phthalate (DIDP)	235	11.6+/-2.1	127.9+/-22.8
Di-n-Hexyl phthalate	178	10.2+/-1.1	112.0+/-11.7
Butyl paraben	83	12.0+/-0.94	108.0+/-8.4
Methyl ethyl ketone	2378	10.2+/-1.9	91.5+/-17.1
Cobalt & cobalt compounds	6927	8.5+/-1.5	84.5+/-14.7
Ethylene glycol monoethyl ester	31	10.3+/-2.4	82.1+/-18.9
Diethyl phthalate	380	8.0+/-0.84	80.0+/8.4
Ethylene glycol	6042	9.8+/-1.9	78.5+/-14.8
Ethyl paraben	97	12.0+/-1.1	35.9+/-3.2
Antimony & Antimony compounds*	3378	10.3 +/1.4	31.0+/04.3
Diisononyl phthalate (DINP)	357	10.3+/-2.1	30.8+/-6.2
Di-n-octyl phthalate (DnOP)	279	9.6+/-0.9	19.3+/-1.8
Octamethylcyclotetrasiloxane	2123	13.9+/-1.6	13.9+/-1.6
Methyl paraben	251	10.2+/-1.2	0
Molybdenum & molybdenum compounds	1617	5.8+/-0.80	0
Phthalic anhydride	137	7.6+/-1.3	0
Propyl paraben	207	11.8+/-0.95	0

Chemical Groups			
Phthalates	3863	10.8+/-2.2	172.5 +/-102.9
Parabens	638	11.2+/-1.4	19.5+/-36.7
Ethylene Glycols	6073	9.8+/-1.9	78.5+/-14.9

Dibutyl phthalate, formaldehyde, DEHP, styrene and butyl benzyl phthalate scored relatively high for both exposure and toxicity scores and are thus found in the upper right-hand quadrant of Figure 1, indicating the most concern. Chemicals not listed as toxicological concerns in any of the resources consulted are found on the Y-axis of Figure 1, see dashed line box. Octamethylcyclotetrasiloxane was assigned an exposure score of 13.9, the second highest. However, the only resource consulted that identified octamethylcyclotetrasiloxane as a toxicological concern was the Global Harmonization System, which classified it as a suspected reproductive and developmental toxicant. Therefore, octamethylcyclotetrasiloxane is found in the upper left-hand quadrant of figure 1, indicating less concern than those chemicals with high exposure scores and high toxicity scores. Chemicals in the bottom left-hand quadrant are the least concerning because they have relatively low exposure and are not classified as toxicologically concerning by the resources consulted for this study. These chemicals are diethyl phthalate, phthalate anhydride and molybdenum.

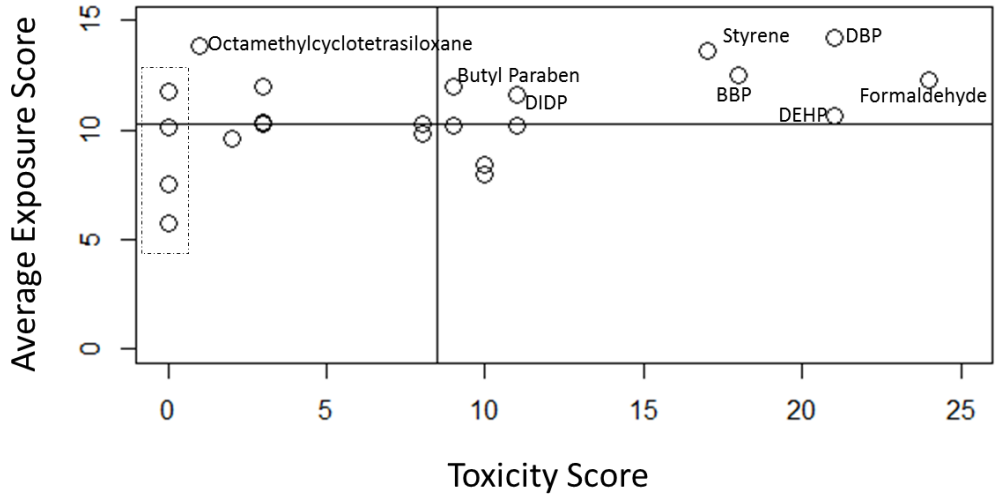

Figure 1: Scatterplot showing the relationship between toxicity and average exposure scores for chemicals in the CSPA framework. The scatterplot is divided into quadrants with lines drawn at the median exposure score (horizontal line) and median toxicity score (vertical line) to emphasize that chemicals relatively high for both toxicity an exposure scores (upper right-hand quadrant) are of higher concern than those with relatively lower scores for both toxicity and potency (lower left-hand quadrant). Formaldehyde, styrene, BBP, DBP and DEHP all fall in the highest priority quadrant in this figure. Other phthalates, DIDP and DNHP also fall in the high priority quadrant. The dashed box on the far left indicates chemicals such as phthalic anhydride, propyl paraben, molybdenum and methyl paraben which were not identified as known toxicants (NT, RD, ED or carcinogens) in any of the databases consulted.

The average total priority index is the product of the toxicity scores and the average exposure scores. Across all records, the average total priority index was 93.1 with a standard deviation of

79.4. The three highest total priority indices are attributed to formaldehyde (average 297.8), dibutyl phthalate (average 294.7) and styrene (average 231.2) (Table 3).

In order to identify underlying relationships among the variables potentially driving the framework results, a principal component analysis (PCA) was conducted. The first two components of the PCA together explained ~56% of the variability in the priority index across chemicals (Figure 2A). Principal component 1 (PC1) explained 33.6% of the variability and is associated with elevated toxicity scores for reproductive and developmental toxicity, carcinogenicity and neurotoxicity. Positive scores for PC1 are also indicative of products designed for children under age three with longer exposure durations and potential oral and inhalation exposure routes (Figure 2B). Negative scores in PC1 are associated with concern over higher chemical concentrations, products applied directly to the skin or body, potential dermal exposure and higher scores for endocrine disruption. Principal component 2 (PC2) explained 23.1% of the variability between chemicals. Positive scores for PC2 are associated with higher reproductive and developmental toxicity and endocrine disruption scores. Positive PC2 scores were also associated with products with potential dermal exposures (Figure 2B). As a result, the solvents (ethylene glycol, ethylene glycol monoethyl ester, methyl ethyl ketone) clustered together with formaldehyde and styrene with positive scores for PC1, indicating concern over neurotoxicity, reproductive and developmental toxicity and carcinogenicity and slightly negative scores for PC2 indicating concern over the concentration of chemicals reported and the product's targeted lifestage. Butyl and ethyl paraben cluster together with negative scores for PC1 and relatively neutral scores for PC2. This indicates higher concern over endocrine disruption, and application directly to the skin or body and potential dermal exposure. Many of the phthalates, such as DEHP, benzyl butyl phthalate, DHNP, Dibutyl phthalate and DIDP cluster together with positive scores for PC2, indicating concern over reproductive and developmental toxicity, endocrine disruption and potential dermal exposure. The phthalates generally cluster away from butyl and ethyl paraben. The separation is due to the presence of both endocrine disruption and reproductive and developmental toxicity for the phthalate cluster and solely endocrine disruption for butyl and ethyl paraben. The lower left-hand quadrant is negative for both PCs and characterized by chemicals that were not recognized as toxic in the sources considered for this study, such as molybdenum, propyl paraben, methyl paraben and phthalic anhydride (Figure 2A). In this quadrant, scores are dominated by lifestage, concentration, and application variables related to exposure characterization.

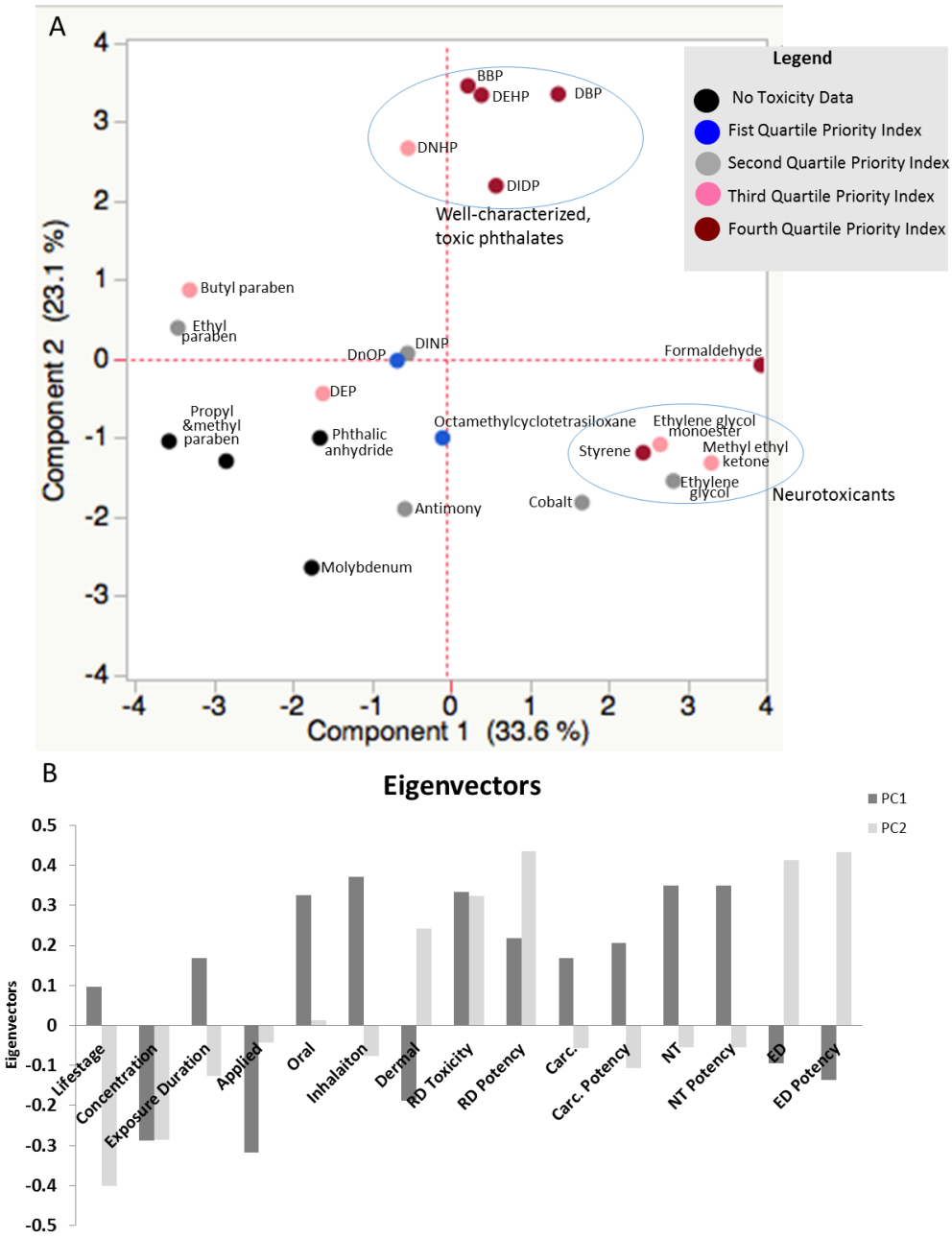

Figure 2A and B: Principal Components Analysis score plot (A) and eigenvector plot (B) for variables in the CSPA framework. The first two principal components explain ~56% of the variability in total priority index between chemicals. A positive value in the score plot shown in Figure 2A for PC1 is associated with elevated concern over reproductive and developmental toxicity (RD), carcinogenicity (Carc.) and neurotoxicity (NT) and an absence or lesser concern about endocrine disruption (ED) as assessed by toxicity scores for each endpoint (shown in Figure 2B). A positive value in the score plot for PC2 indicates greater concern over reproductive and developmental toxicity, and endocrine effects, as well as an absence or lesser concern over carcinogenicity. Chemicals that cluster together share toxicities. For example, organic solvents such as methyl ethyl ketone and ethylene glycol, cluster with other known neurotoxicants, such as styrene. Phthalates that are well-characterized endocrine disruptors and reproductive and developmental toxicants cluster together as well.

The total priority index and exposure score can also be used to identify high priority product categories. Table 4 summarizes the exposure scores and total priority indices across the product segments reported in the CSPA database. Kitchen merchandise, stationary/office machinery/occasion supplies and toys/games had the highest total priority indices. In each of these categories, formaldehyde, phthalates (as a group) and styrene had the highest priority indices. Together, kitchen merchandise, stationary/office machinery/occasion supplies and toys/games comprise approximately 16% of all CPSA reports. Almost half (44%) of reports fall under the clothing product segment. The three highest scoring chemicals in this category are formaldehyde (total priority index average of 264.8), styrene (total priority index average of 209.1) and phthalates (as a group, total priority index of 134.1). These results are shown in an expanded version of Table 4 available as supplemental Table S3.

Table 4: Average total priority indices and exposure scores across product segments. Total number of reports in each product segment are also shown.

Product Segments	**Total Priority Index**	**Exposure Score**	**Total number of reports**
Kitchen Merchandise	205.8	12.2	72
Stationery/Office Machinery/Occasion Supplies	158.6	10.1	365
Toys/Games	131.9	13.0	4910
Arts/Crafts/Needlework	105.3	9.3	631
Household/Office Furniture/Furnishings	105.1	10.7	1446
Baby Care	103.8	10.7	991
Footwear	90.5	10.0	4940
Personal Accessories	82.3	9.0	1229
Clothing	79.2	9.3	14551
Camping	71.1	8.9	87
Beauty/Personal Care/Hygiene	42.4	10.2	559

We compared the CSPA framework exposure and endocrine disruptor scores with ExpoCast and ToxCast, respectively. The CSPA endocrine disruptor score was calculated by the classification and the LOAEL reported in the European Chemical Agency's Endocrine Disruptor Substances of Concern database (Table S2) as well as the exposure score based on chemical and product properties. Filer et al., 2014, applied ToxPi for the priortization of endocrine disruptors based on the phase 2 ToxCast in vitro assays and chemical properties that are associated with exposure potential. Eight of the ten chemicals identified as endocrine disruptors in this framework and six chemicals included in this framework but not identified as endocrine disruptors had ToxPis calculated by Filer et al. 2014. Butyl paraben scored high for endocrine disruption in both ToxPi and through the CSPA framework. However, other chemicals such as DEHP and DBP scored relatively higher through the CSPA framework than through the ToxPi predictions. Octamethyltetrasiloxane and propyl paraben score high using ToxPi, but are not identified as endocrine disruptors in the resources consulted for this study.

ExpoCast predicts exposure to environmental chemicals at the population level [42]. While many chemicals found in consumer products are have predicted exposure ranges in ExpoCast,

other potential exposure routes are also considered. Octamethylcyclotetrasiloxane has one of the highest exposure scores and a higher predicted exposure in ExpoCast, relative to the other chemicals considered (Figure 2B). Other chemicals, like styrene, have higher exposure scores relative to those predicted using ExpoCast. Two phthalates, DINP and DEHP have higher median exposure predictions in ExpoCast relative to their exposure scores from the CSPA framework. This may be due to the fact that, in the United States, these chemicals are more tightly regulated in children's products than in general consumer products.

Table 5 summarizes the top three chemicals according to each prioritization strategy: CSPA reporting frequency, CSPA total priority index, CSPA exposure score, ExpoCast, ToxPi endocrine disruptor score and CSPA endocrine disruptor score. When CSPA chemicals are prioritized based only on frequency of reports, cobalt and cobalt compounds, antimony and antimony compounds and ethylene glycol are prioritized. However, when the toxicity, toxicokinetics and exposure patterns are considered through the CSPA total priority index, formaldehyde, dibutyl phthalate and styrene are prioritized. The total number of reports of these three chemicals combined comprise approximately 15% of total CSPA reports during the time period assessed. Butyl paraben is identified as a high priority endocrine disruptor based on it scoring in the top three chemicals using both the CSPA endocrine disruptor score and the ToxPi score. ExpoCast and CPSA Exposure scores both identify octamethylcyclotetrasiloxane.

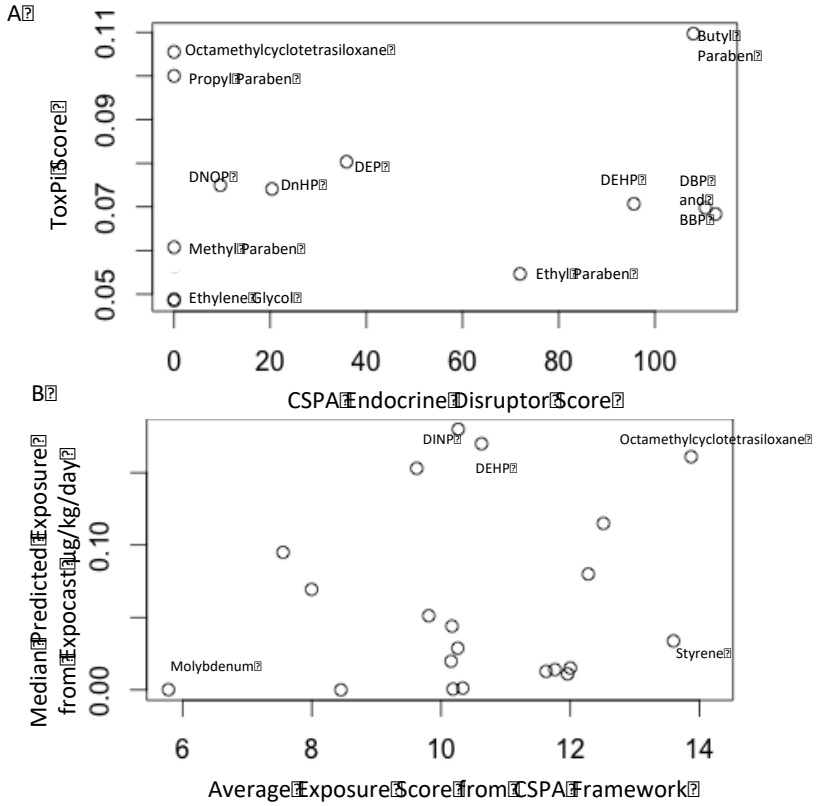

Figure 3a and b: Comparison of CSPA endocrine disruptor score to ToxPi scores (A) and comparison of CSPA exposure score to ExpoCast score (B). Butyl paraben scores relatively high using both the CSPA endocrine disruptor score and the ToxPi score. DEHP and DBP score higher using the CSPA framework than using ToxPi. Some chemicals, such as octamethylcyclotetrasiloxane and propyl paraben, score relatively high using ToxPi but are not

classified as endocrine disruptors using the CSPA framework. Some chemicals, such as octamethylcyclotetrasiloxane, have relatively high ExpoCast predictions and score higher using the CSPA framework for average exposure scores. Other chemicals, such as the phthalates DINP and DEHP, have higher exposure predictions from ExpoCast than exposure scores using the CSPA framework.

Table 5: Summary of prioritization tools, basis and the three highest scoring chemicals.

Prioritization Tool	Basis	Top Three Chemicals
Total number of reports in CSPA	Frequency of chemical reports	Cobalt and cobalt compounds, ethylene glycol and antimony and antimony compounds
CSPA Total Priority Index	Exposure potential, chemical properties, neurodevelopment, carcinogenicity, endocrine disruption, reproductive and developmental toxicity.	Formaldehyde, dibutyl phthalate and styrene
CSPA Endocrine Disruptor Score	Exposure potential, chemical properties, endocrine disruption based on databases largely comprised of *in vivo* studies	Butyl paraben, dibutyl phthalate and butyl benzyl phthalate
ToxPi Endocrine Disruption Score	Chemical properties, endocrine disruption based on *in vitro* assays	Butyl paraben, propyl paraben and octamethylcyclotetrasiloxane
CSPA Exposure Score	Lifestage, product description, chemical properties, toxicokinetics and potential exposure routes	Formaldehyde, octamethylcyclotetrasiloxane and styrene
ExpoCast	Prediction of exposure from all routes	Diisononyl phthalate, Di-2-ethylhexyl phthalate and octamethylcyclotetrasiloxane

4. Discussion

The goal of this framework was to identify and prioritize chemicals in the CSPA database for further consideration and to compare the results with other prioritization methods, such as ToxCast and ExpoCast. In order to do this, it was necessary to understand the context surrounding the potential exposure and the toxicity and potency of the chemical. We used the target age group and product segment descriptions to identify potential exposure routes and durations and combined this information with the concentration to provide context surrounding the exposure. Chemical properties and absorption parameters were used to incorporate toxicokinetics. Toxicity and potency were calculated using a wide array of curated databases (Table 1, 2 S2). By combining these parameters in a multi-attribute utility function, we were able to calculate a total priority index for each of the ~33K CSPA records related to the most frequently reported chemical groups, about 88% of all CSPA records to date.

Two methods were used to identify priority chemicals in the CSPA database from this framework. Exposure scores and toxicity scores were plotted to identify chemicals notable in both dimensions. This method identified formaldehyde, styrene, dibutyl phthalate (DBP), butyl benzyl phthalate (BBP), di-2-ethylhexyl phthalates (DEHP), diisodecyl phthalate (DIDP) and butyl paraben as priority chemicals. The second method for identifying priority chemicals was through the calculation of a total priority index, which is the product of the exposure and toxicity scores. This method identified formaldehyde, DBP, styrene, BBP and DEHP as the highest priority chemicals. With the exception of BBP, which is considered a reproductive and developmental toxicant and an endocrine disruptor, the other five highest priority chemicals were considered toxic for three out of the four endpoints considered in this framework. A PCA confirmed the observation that toxicity drives a substantial part of the variability between chemicals. Neurotoxicants, such as formaldehyde, styrene, methyl ethyl ketone and ethylene glycol clustered together while the phthalates known for both endocrine disruption and reproductive and developmental toxicity clustered together, separate from compounds known for endocrine disruption alone. Formaldehyde did not cluster as close to styrene as was expected. Both chemicals are characterized by reproductive and developmental toxicity, neurotoxicity and carcinogenicity, however, they have varying scores related to dermal and oral toxicokinetics. This exemplifies the importance of including exposure routes, toxicokinetics and toxicity in one framework. The other prioritization frameworks examined in this study focused on toxicity (ToxPi) or exposure (ExpoCast), therefore combination of exposure and toxicity is a unique and important feature of this framework.

The CPSA framework can be used to identify individual chemicals or chemical groups of high priority to children's environmental health. In this analysis, the three chemicals with the highest total priority indices, when phthalates and parabens were grouped were formaldehyde, phthalates and styrene. Individually, formaldehyde, styrene and dibutyl phthalate had the highest total priority indices. While analysis of individual chemicals can help identify potential issues related to regrettable substitutions, consideration of phthalates and parabens as groups may be relevant to regulations that may approach chemicals as groups, taking a more holistic view of toxicity since many phthalates and parabens have similar mechanisms of toxicity.

The chemical groups with the highest average total priority indices were formaldehyde, phthalates and styrene. While the CSPA framework is not weighted by reporting frequency, reports for these chemicals comprised approximately 15% of total reports. Thus, the magnitude of exposure potential from these products is not inconsequential. Formaldehyde, phthalates and styrene were also identified as high priority chemicals when average total priority indices were compared across product segments. Kitchen merchandise, stationary/office machinery/occasion supplies and toy/games were the three product segments with the highest average total priority indices. Within each of these segments, formaldehyde, phthalates and styrene were the highest priority chemicals.

The results of this framework were compared to other prioritization tools such as ExpoCast and ToxPi. While the CSPA framework relies on curated databases for toxicological assessment, ToxPi uses high throughput data from the in vitro assays publicly available through the ToxCast database. The comparison demonstrated the benefits and drawbacks to both approaches. For example, ToxPi was able to calculate scores for more endocrine disrupting chemicals than the

curated database (ECHA Existing Substance Endocrine Disruptor Database) used to calculated the CSPA endocrine disruption score. Octamethylcyclotetrasiloxane is an example of a chemical that was poorly characterized in available databases, but scored high for endocrine disruption using in vitro assays. However, regulatory decisions for future action on CSPA chemicals rely on the presence of a substantial body of evidence. Therefore, the benefit to using the CSPA framework with curated databases, allows for a stronger degree of confidence in the toxicological assessments. As the ToxCast assays continue to be more widely applied and more adverse outcome pathways are created, this high-throughput approach will provide added value.

ExpoCast was the other high throughput prioritization tool included in this analysis. The relationship between the CSPA exposure score and ExpoCast exposure prediction is highly variable. While some chemicals, such as octamethylcyclotetrasiloxane and molybdenum are relatively consistent between the two scores, other chemicals, such as styrene, had vastly different exposure scores between the CSPA framework and ExpoCast. Styrene has a high exposure score from the CSPA framework and a much lower ExpoCast prediction. This is partially due to differences in how the exposure scores are calculated relative to ExpoCast. The exposure score is only based on the potential for exposure from children's products reported in the CSPA database, while the ExpoCast prediction includes multiple exposure sources. Additionally, while frequency of chemical reporting was not included as a variable in the CSPA exposure score, chemicals were selected for inclusion in the framework based on the number of reports. Therefore, the CSPA exposure score is not explicitly weighted for production volume. Expocast, on the other hand, relies on chemical use estimations [42]. DINP and DEHP have moderate CSPA exposure scores and high ExpoCast predictions. This could be related to US consumer product laws, which limit the permissible concentration of some phthalates in children's products, but not consumer products as a whole.

This is the first framework developed for the toxicological interpretation of the CSPA data. The benefits to using this framework include the relatively high amount of context regarding exposures and the detailed chemical and toxicological properties, including potency considered. Because the CSPA database comprises over 33,000 records as of September, 2015, the relatively high throughput capacity of the framework is important. Lifestage, exposure duration, exposure route, application to skin or body and concentration were all derived directly from the fields in the CSPA database. This allowed for the relatively quick processing of the extensive database. Additionally, because all information was derived directly from the CSPA database or based on chemical properties that were widely available, there were no missing data for the exposure score. This allows for the identification of chemicals with high exposure potential and less well characterized toxicity. Some chemicals, such as phthalic anhydride, propyl paraben, methyl paraben and molybdenum, were not classified as toxic for the endpoints considered in this framework in any of the databases and resources consulted. These chemicals were included in the CSPA database, but did not receive toxicity scores because they were toxic to biological systems not considered in this framework, were toxicologically characterized by databases not included in this framework, REPROTEXT [46] or were included as part of a larger group of chemicals. This lack of data can lead to lower total priority indices that are not necessarily indicative of safety. However, because the exposure score is complete in all cases, it can be used to identify chemicals, such as octamethylcyclotetrasiloxane, that have high exposure potential from children's products but may be poorly characterized in the databases considered.

Octamethylcyclotetrasiloxane is an example of a chemical in need of further characterization in the curated databases considered for this study. Both ExpoCast and the CSPA exposure score identify octamethylcyclotetrasiloxane as having high potential for exposure. Additionally, its high ToxPi score suggests that octamethylcyclotetrasiloxane could be a potent endocrine disruptor.

Washington State was among the first to require reporting of chemicals of concern in children's products. Since then, other states have begun to implement similar requirements. While Washington has developed an extensive database to help guide future regulatory action, improvements to the reporting structure of the CSPA database could expand the toxicological interpretation of the data. For example, metals such as molybdenum, cobalt and antimony are reported by total elemental amount. There are significant differences in toxicities and toxicokinetics between metalloid compounds. Because metalloid compounds were not specified in the CSPA database, the unique features of specific metal compounds are not reflected in the CSPA framework and may compromise the ability to accurately assess the toxicities and toxicokinetics associated with the presence of antimony, cobalt and molybdenum in children's products. Additionally, more information regarding when the laboratory tests were performed by the manufacturers would help determine whether volatile chemicals reported as "contaminants" are likely to off-gas by the time the product reaches the consumer.

The CSPA framework presented here provides a method for processing large amounts of consumer product data in a relatively high content manner. However, one limitation of this approach is that it does not calculate a comparable risk between chemicals but, rather ranks the chemicals in the CSPA database. Thus a total priority index of 100 is not 10 times more concerning than a total priority index of 10. This decision was made to allow the database to be processed in a relatively high throughput manner. The total priority index focuses on exposure potential from product use as well as exposure potential from house-dust as the product disintegrates. While it includes chemical properties to account for absorption, bioaccumulation is not included. No persistent organic pollutants were among the chemicals used in this analysis. However, persistent organic pollutants are included in the CSPA database as a whole. Inclusion of this additional data and bioaccumulation factors, may modify the high priority chemicals identified using this framework. To account for some of the limitations of the CSPA framework, it is recommended that this approach is employed along with other prioritization tools, such as ToxPi and ExpoCast. High throughput frameworks can also be used in conjunction with expert judgment and stakeholder feedback to ensure that the resulting chemical priorities are reflective of the regulatory question and context surrounding the prioritization needs.

5. Conclusions:

Overall, this framework provides one method of prioritizing chemicals and products that may be of concern for children's health. Based on the results of this framework, formaldehyde, DBP and styrene should be considered for future action to help reduce the potential for children's exposure through commercial products. When parabens and phthalates are considered as groups, phthalates rise to the top along with formaldehyde and styrene. Other prioritization tools, such as ToxPi, suggest prioritization of parabens and octamethylcyclotetrasiloxane. These recommendations should be taken into account as regulatory agencies plan future strategies to protect children's health.

Supplementary Materials: The following are available online at www.mdpi.com/link, Table S1: Total number of reports in the CSPA database from August 2012 to September 2015 by chemical. Table S2: Potency factor scores and sources and Table S3: Total priority indices, exposure scores and number of reports by product segment (gray shaded rows) and broken down by chemical groups.

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Supplemental Information for Chapter 1:

Supplemental Table S1: Total number of reports in the CSPA database from August 2012 to September 2015 by chemical. Chemicals shown in gray are included in the analyses for this paper. These chemicals represent approximately 88% of the database as a whole.

Chemicals	**Number of Reports**
Cobalt & cobalt compounds	6927
Ethylene glycol	6042
Antimony & Antimony compounds	3378
Methyl ethyl ketone	2378
Styrene	2251
Octamethylcyclotetrasiloxane	2123
Molybdenum & molybdenum compounds	1617
Di-2-ethylhexyl phthalate	909
Dibutyl phthalate	778
Butyl benzyl phthalate (BBP)	610
Formaldehyde	533
Toluene	495
Ethylbenzene	458
Arsenic & Arsenic compounds arsenic trioxide (1327-53-3) & dimethyl arsenic (75-60-5)	387
Diethyl phthalate	380
Diisononyl phthalate (DINP)	357
4-Nonylphenol; 4-NP and its isomer mixtures CAS 84852-15-3 and CAS 25154-52-3	338
Cadmium & cadmium compounds	282
Di-n-octyl phthalate (DnOP)	279
Methyl paraben	251
Diisodecyl phthalate (DIDP)	235
Acetaldehyde	216
Propyl paraben	207
Di-n-Hexyl phthalate	178
C.I. solvent yellow 14	172
Mercury & mercury compounds including methyl mercury (22967-92-6)	165
2-Ethylhexanoic acid	154
Phenol	140
Phthalic anhydride	137
Ethyl paraben	97
n-Butanol	95
Bisphenol A	87
Butyl paraben	83
Acrylonitrile	73
Methylene chloride	70

Tetrabromobisphenol A	62
Vinyl chloride	52
Aniline	45
Carbon disulfide	42
2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether; BDE-209	41
3,3'-Dimethylbenzidine and Dyes Metabolized to 3,3'-Dimethylbenzidine	39
Benzene	37
2-Ethyl-hexyl-4-methoxycinnamate	32
Ethylene glycol monoethyl ester	31
p-Hydroxybenzoic acid	31
Estragole	28
2-Methoxyethanol	26
4-tert-Octylphenol; 1,1,3,3-Tetramethyl-4-butylphenol	23
Tris(2-chloroethyl) phosphate	23
Hexachlorobutadiene	21
N-Methylpyrrolidone	21
2,4-Diaminotoluene	20
Perfluorooctanyl sulphonic acid and its salts; PFOS	20
1,4-Dioxane	19
Phenol, 4-octyl-	19
2-Aminotoluene	18
Hexabromocyclododecane	18
N-Nitrosodimethylamine	18
N-Nitrosodiphenylamine	18
Perchloroethylene	18
1,1,2,2-Tetrachloroethane	17
para-Chloroaniline	17
Benzene, pentachloro	16
Butylated hydroxyanisole; BHA	16
Hexachlorobenzene	14
Tris(1,3-dichloro-2-propyl)phosphate	5
Benzophenone-2 (Bp-2); 2,2',4,4'-Tetrahydroxybenzophenone	3
Total Number of Records	33692

Supplemental Table S2: Potency factor scores and sources for reproductive and developmental toxicants and endocrine disruptors

Chemical	Reproductive and Developmental Toxicants			Endocrine Disruptors			
	NOAEL	**Score**	**Endpoint Examined and Reference**	**Reported LOAEL**	**Calculated NOAEL**	**Score**	**Endpoint Examined and Reference**
Butyl benzyl phthalate (BBP)	50 mg/kg bw/day	3	Anogenital distance (AGD) in both F1 and F2*	1000 mg/kg/day	100	3	Testis impacts #
Butyl Paraben				100 mg/kg/day	10	3	Decreased sperm count#
Di-2-ethylhexyl phthalate	4.8 mg/kg/day	3	Irreversible testis damage*	52 mg/kg/day	5.2	3	Induction of peroxisome proliferation#
Dibutyl phthalate	52 mg/kg bw	3	Embryotoxicity*	50 mg/kg/day	5	3	Testis decreased weight # or increased weight #
Diethyl phthalate				2000 mg/kg/day	200	3	Leydig cell ultra structural alterations#
Diisodecyl phthalate (DIDP)	33 mg/kg/d	3	Decreased offspring survival*				
Diisononyl phthalate (DINP)	200 mg/kg/day	3	Fetal toxicity*				
Di-n-Hexyl phthalate	38 mg/kg/day	3	Based on 380 mg/kg/day LOAEL^				
Ethyl Paraben				1000 mg/kg/day	1000	1	NOEL for sex hormone secretion#
Methyl Ethyl Ketone	594 mg/kg-day	1	Based on 0.6 RfD with a 1000 fold uncertainty factor. Study endpoint was decreased Pup Body Weight$				

* From ECHA Existing Substances Database, $From EPA IRIS, ^From NTP, # From ECHA Substances of Concern Database

Supplemental Table S3: Total priority indices, exposure scores and number of reports by product segment (gray shaded rows) are broken down by chemical groups. The three chemicals with the highest average priority index are shaded in light red. In every case except beauty/personal care/hygiene, formaldehyde, phthalates and styrene had the highest average total priority indices. Methyl ethyl ketone, formaldehyde and styrene had the highest average total priority indices for beauty/personal/care/hygiene products.

	Average Priority Index	**Average Exposure Score**	**Number of Reports**
Arts/Crafts/Needlework	105.3	9.3	631
Antimony & Antimony compounds	27.0	9.0	93
Cobalt & cobalt compounds	70.0	7.0	25
Ethylene glycol	64.0	8.0	64
Formaldehyde	241.5	11.5	28
Methyl ethyl ketone	76.5	8.5	26
Molybdenum & molybdenum compounds	0.0	5.0	27
Octamethylcyclotetrasiloxane	13.0	13.0	12
Parabens	12.0	10.0	80
Phthalates	168.3	9.4	211
Styrene	195.5	11.5	65
Baby Care	103.8	10.7	991
Antimony & Antimony compounds	31.4	10.5	110
Cobalt & cobalt compounds	91.3	9.1	174
Ethylene glycol	85.3	10.7	170
Formaldehyde	294.0	14.0	18
Methyl ethyl ketone	100.0	11.1	55

Molybdenum & molybdenum compounds	0.0	6.0	55
Octamethylcyclotetrasiloxane	13.8	13.8	45
Parabens	12.4	11.5	29
Phthalates	158.4	11.3	263
Styrene	216.3	12.7	72
Beauty/Personal Care/Hygiene	42.4	10.2	559
Antimony & Antimony compounds	28.8	9.6	36
Cobalt & cobalt compounds	70.0	7.0	30
Ethylene glycol	68.2	8.5	43
Formaldehyde	243.9	11.6	22
Methyl ethyl ketone	76.5	8.5	12
Octamethylcyclotetrasiloxane	13.0	13.0	12
Parabens	17.5	10.9	359
Phthalates	73.0	7.4	32
Styrene	198.1	11.7	13
Camping	71.1	8.9	87
Antimony & Antimony compounds	30.6	10.2	5
Cobalt & cobalt compounds	82.5	8.3	32
Ethylene glycol	76.8	9.6	25
Methyl ethyl ketone	76.5	8.5	7
Molybdenum & molybdenum compounds	0.0	5.4	10
Octamethylcyclotetrasiloxane	13.0	13.0	4
Styrene	221.0	13.0	4
Clothing	79.2	9.3	14551

Antimony & Antimony compounds	29.2	9.7	1703
Cobalt & cobalt compounds	81.3	8.1	4329
Ethylene glycol	75.1	9.4	3691
Formaldehyde	264.8	12.6	185
Methyl ethyl ketone	87.0	9.7	928
Molybdenum & molybdenum compounds	0.0	5.6	879
Octamethylcyclotetrasiloxane	13.5	13.5	805
Parabens	35.7	11.6	57
Phthalates	134.1	10.0	1092
Styrene	209.1	12.3	882
Footwear	90.5	10.0	4940
Antimony & Antimony compounds	29.2	9.7	322
Cobalt & cobalt compounds	80.9	8.1	922
Ethylene glycol	74.8	9.3	804
Formaldehyde	253.2	12.1	18
Methyl ethyl ketone	88.7	9.9	785
Molybdenum & molybdenum compounds	0.0	5.5	190
Octamethylcyclotetrasiloxane	13.6	13.6	753
Parabens	33.0	10.5	8
Phthalates	187.6	10.2	909
Styrene	208.2	12.2	229
Household/Office Furniture/Furnishings	105.1	10.7	1446
Antimony & Antimony compounds	30.7	10.2	165
Cobalt & cobalt compounds	86.5	8.6	238

Ethylene glycol	79.6	10.0	234
Formaldehyde	269.5	12.8	73
Methyl ethyl ketone	99.0	11.0	141
Molybdenum & molybdenum compounds	0.0	5.9	64
Octamethylcyclotetrasiloxane	14.0	14.0	141
Parabens	36.0	11.8	4
Phthalates	177.0	11.3	297
Styrene	217.0	12.8	89
Kitchen Merchandise	205.8	12.2	72
Antimony & Antimony compounds	31.5	10.5	6
Cobalt & cobalt compounds	90.0	9.0	4
Formaldehyde	294.0	14.0	12
Molybdenum & molybdenum compounds	0.0	6.0	2
Parabens	0.0	11.0	1
Phthalates	232.0	12.2	32
Styrene	221.0	13.0	15
Personal Accessories	82.3	9.0	1229
Antimony & Antimony compounds	27.6	9.2	88
Cobalt & cobalt compounds	73.1	7.3	294
Ethylene glycol	67.6	8.5	236
Formaldehyde	241.5	11.5	22
Methyl ethyl ketone	80.6	9.0	137
Molybdenum & molybdenum compounds	0.0	5.1	90
Octamethylcyclotetrasiloxane	13.2	13.2	107

Phthalates	142.4	9.6	127
Styrene	198.5	11.7	128
Stationery/Office Machinery/Occasion Supplies	158.6	10.1	365
Antimony & Antimony compounds	28.0	9.3	37
Cobalt & cobalt compounds	73.8	7.4	24
Ethylene glycol	64.0	8.0	25
Formaldehyde	284.6	13.6	10
Methyl ethyl ketone	76.5	8.5	17
Molybdenum & molybdenum compounds	0.0	5.0	10
Octamethylcyclotetrasiloxane	13.0	13.0	12
Parabens	0.0	10.2	5
Phthalates	220.5	10.6	199
Styrene	203.7	12.0	26
Toys/Games	131.9	13.0	4910
Antimony & Antimony compounds	36.5	12.2	813
Cobalt & cobalt compounds	108.0	10.8	855
Ethylene glycol	102.1	12.8	781
Formaldehyde	389.1	18.5	145
Methyl ethyl ketone	118.5	13.2	270
Molybdenum & molybdenum compounds	0.0	6.9	290
Octamethylcyclotetrasiloxane	16.6	16.6	232
Parabens	25.4	13.1	95
Phthalates	210.9	13.4	701
Styrene	279.0	16.4	728

CHAPTER 2:

Title: Required Reporting and Product Testing Databases for Toxic Chemicals in Children's Consumer Products

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Abstract

Toxic chemicals in children's consumer products can impair child health and development. These concerns have led to the implementation of children's product reporting frameworks in multiple jurisdictions throughout the United States and internationally. Washington State enacted the Children's Safe Product Act (CSPA) in 2009 which requires manufactures to report the presence of 88 chemicals of high concern to children in any product sold or manufactured in Washington State (CSPA Manufacturers Database (CSPA-MD). This law also restricts (prohibits, limits) the presence of thirteen chemicals (lead, cadmium, 6 phthalates, and 5 flame retardants). Washington State also maintains a Product Testing Database (PTD) in which children's products are purchased and tested for chemicals of high concern to children. This project aimed to compare the two databases to determine whether there are systematic differences in the product chemical combinations included in each database and whether the concentrations reported are different. We compared 40,204 records from the CSPA-MD and 8,344 records from the PTD. Individual records were merged to compare averages within each product-family chemical combination for which we had 373 from the CSPA-MD and 365 from the PTD. Overall, 63% of product-family chemical combinations detected in the PTD in at least one analysis were reported by manufacturers. Of the product-family chemical combinations detected by the state and reported by manufacturers, the manufactures reported higher concentrations in 69-84% of product family chemical comparisons. For restricted chemicals, manufacturers reported higher concentrations in 59% of the product family chemical comparisons. While manufactures reporting higher concentrations may seem counter intuitive, this is reflective of the law. CSPA requires manufactures to report the highest concentration found.

Key words: Children's Health, Consumer Products, Policy, Phthalates, Endocrine Disruption

1. Introduction

Children are uniquely susceptible to the myriad of environmental toxicants they are exposed to throughout development [1], many of which have not been fully evaluated for developmental, neurological, and other toxicities [2]. Consumer products represent an important exposure source for many toxicants due to their intended uses which lead to direct contact with children [2-6]. Examples of chemicals found in children's products include phthalates [4, 7], and flame-retardants [7, 8], cadmium [9] and lead [5, 10]. In addition to the extensive array of chemicals found in children's products, the unique ways in which children interact with their environments and their increased biological susceptibility contribute to concerns about potential health impacts. Hand-to-mouth behavior is common among young children and increases the time a product may be in a child's mouth, consequently, increasing oral exposure potential [11]. Children also spend more time on or near the floor [11], increasing exposure to inhaled or ingested house dust, which can act as a reservoir for chemicals often derived from consumer products [12-17]. Furthermore, because of their small body size, the dose associated with these exposures is proportionately greater than the dose adults receive [11].

In response to potentially toxic chemicals found in consumer products, the Children's Safe Product Act (CSPA), passed in 2006. Manufacturers must report the concentration range (presence) of 88 chemicals of high concern in children's products sold in WA to the Department of Ecology's reporting database... The CSPA manufacturers database (CSPA-MD) contains over 55,000 records as of August 2018. Manufacturers are required to report the concentration range, product description, intended age for product use, chemical function, date and manufacturer for any children's product containing any of the 88 chemicals of high concern to children. Three of the primary limitations of this reporting structure are that i) manufacturers do not report products that tested negative for chemicals of high concern to children; ii) the reported product description does not allow for identification of specific products and iii) concentrations are reported in broad ranges that are not related to chemical potency. These limitations lead to uncertainty surrounding the actual concentrations of toxic chemicals in children's consumer products.

Unique to Washington state is the product-testing database (PTD), which contains results from analyses of chemicals found in consumer products. The PTD reports specific concentrations, laboratory methods and the level of detection [18] run by the Washington State Department of Ecology. Limitations of the product testing database are that not all products are not randomly selected for analysis and not all chemicals of high concern to children have been analyzed. The goal of the analyses is to enforce existing law and identify priorities for future actions. This biases the database towards inclusion of products likely to have higher concentrations of toxic chemicals.

The objective of this project was to assess the alignment between the two databases both in detection rates and concentrations detected.

2. Methods

2.1 Database access: The CSPA manufacturers database (CSPA-MD) was downloaded from https://fortress.wa.gov/ecy/cspareporting/Reports/ReportViewer.aspx?ReportName=GetAllReport on 7/23/2018. These represent the manufacturers reports that have been subject to Ecology outreach efforts. If manufacturers report concentrations of restricted chemicals above the limit, Ecology staff reach out to manufacturers to double check accuracy.

The product testing database (PTD) was accessed from: https://fortress.wa.gov/ecy/ptdbpublicreporting/Reports/ReportViewer.aspx?ReportName=RawDataReport on 8/2/2018. All studies related to children's products were included: Mattel, Flame Retardants NEP 140421, Metals and Phthalates, Supplemental Flame Retardants, CHHC 1503039, Christmas 2014, Valentines Day, Hg and PVC, Easter, 4th of July, Back to school, Halloween, Metals in Jewelry, Christmas 2015, CHCC and Formaldehyde, D4, MEK, and Styrene in Children's Products. The study on Formaldehyde, D4, MEK, and Styrene in Children's Products was accessed through personal communication with Department of Ecology. Data flagged with "E", "NJ" and "REJ" were dropped as these indicated issues with quality assurance parameters. A total of 20 product-family chemical combinations contained records with QC flags, 19 of these combinations also contained records without QC flags, which were included in the analysis.

2.2 Comparison of detection rates: In order to merge the two databases, we matched records by product family and chemical. Chemicals not tested in the PTD or not required to be reported by manufacturers were excluded. In both databases, products are described using a hierarchical system of segment, family, class and brick. With segment being the least granular and brick being the most granular. An example segment is "Baby Care" and an example brick is "pacifiers/ teething rings." There were some differences in brick nomenclature between the PTD and CSPA-MD and non-matches were excluded. For the purposes of this analysis a record refers to a measurement or report of a specific chemical in a specific product. Product-family chemical combinations refer to the average concentration of a specific chemical within a specific product family (e.g. DEHP in baby care products). Product-family chemical matches refer to instances where the CSPA-MD and PTD both contain the specific chemical in a specific product family. Product-family chemical combinations may contain multiple records. We selected product-family-chemical combinations as the unit for further analysis because compared to brick or class level matching, there were more records within each product-chemical combination. The number of records within each product family chemical group is shown in Table 1. Supplemental Table 1 shows the number of records within each match using the product brick and class description. Unique and shared product family chemical combinations were identified in order to compare detects and reports between the two databases. Non-detects were identified within the PTD through the "U" and "UJ" codes. Product- family chemical combinations that were detected by the state but not reported by manufacturers were identified as well as product-chemical combinations that were reported by manufacturers and measured, but not detected by the state. Because this project examined unique and common product-chemical combinations, there were some cases where a product chemical combination contained both detects and non-detects as multiple analyses were done.

2.3 Comparison of concentrations reported and detected: Within the CSPA-MD, chemical concentrations are reported in 6 ranges (Table 2), thus, we calculate the average concentration for each product-chemical combination using the low end of the range, the midpoint and the high end of the range. The lowest range is from the Practical Quantification Level (PQL) to 100ppm. The PQL is defined as the "lowest concentration that can be reliably measured within specified limits of precision, accuracy, representativeness, completeness, and comparability during routine laboratory operating conditions" and is specified within Ecology guidance [19]. For the low end of the range calculations, the data was set to the PQL. The midpoint of the

lowest range was calculated for each chemical as the midpoint between the individual PQL and 100ppm. We assigned the midpoint and the high value of the highest manufacturer's range (equal to or greater than 10,000 ppm) the average of the state data concentrations where the ppm exceeded 10,000. The distribution of PTD data within each of the CSPA-MD concentration ranges is shown in Figure S1. In order to compare chemical concentrations between the two databases, product family chemical combinations were matched using only PTD detects and CSPA-MD reports. Additional analyses were conducted on a subset of chemicals restricted in children's products to determine whether under/over reporting rates among chemicals restricted in children's products are different than all chemicals. Restricted chemicals included: 6 phthalates, 5 brominated flame retardants, and cadmium. While lead is restricted in children's products, it is not a required reporting chemical under CSPA and was thus excluded from this analysis. We also analyzed the data by chemical function to determine whether chemicals that were intentionally added were reported more accurately than those reported by manufacturers to be contaminants. Contaminants were identified by whether the manufacturers reported the function to be "No function- contaminant" or "Source contaminant."

Datasets were merged and figures were developed using R program with the packages dplyr and ggplot2.

3. Results

The overlap in product family chemical combinations between the two databases is shown in Table 3. Of the 373 unique product-family chemical combinations reported by manufacturers, eight were included in the PTD as detects 100% of the analyses, 130 were included in PTD as detects in at least one of their analyses, 128 product family combinations were included as non-detects in the PTD and 107 product family chemical combinations were not included PTD (Table 3). Overall 73% of the product family chemical combinations included as detects in the PTD in 100% of the analyses were reported by manufactures. Of the product family chemical combination with both detects and non-detects in the PTD, 87% were reported by manufacturers. Of the product family chemical combinations included exclusively as non-detects in the PTD, 63% were reported by manufacturers. Of the 180 unique product-family chemical combinations detected in the PTD, all except for three were reported by manufacturers in the CSPA-MD. Arsenic, was measured beauty/personal care/hygiene variety packs above the 3 ppm limit set by the Federal Food and Drug Administration. Cadmium was measured in Beauty/Personal Care/Hygiene Variety Packs and Stationery/Office Machinery. CSPA limits Cadmium in children's products to 40ppm. The concentration measured in Beauty/Personal Care/Hygiene Variety Packs was above that threshold.

When product components were added to the matching criteria, there was an increase in the overall number of matches, due to more possible unique combinations, but a decrease in the number of records per combination (Table 2). Of the 202 product family component chemical combination detected in the PTD, 70% were reported by manufacturers. 48% of the product family component combination measured, but not detected by the state, were reported by manufacturers. Twenty-one product family component combinations were detected in all the state analyses but not reported by manufacturers (Table 4 and Table S2).

The average concentration of PTD (detects only) and CSPA-MD (reports only) product family chemical combinations (using the midpoint of the concentrations ranges) grouped by chemical (Figure 1A) and product family (Figure 1B) shows PTD concentrations are frequently lower

than CSPA-MD concentrations. The ten product-chemical combinations with the largest differences in concentrations between the two databases are shown in Table 5.

We found that overall, 18% of product-family chemical combinations had lower concentrations in the CSPA-MD (using the midpoint of the range) than in the PTD (Table 6). When we used the low or high end of the range reported by manufactures, 30% (low end of range) to 18% (high end of range) of the manufacturer reports were lower than the concentration in the PTD. Among chemicals restricted in children's products, 41% had lower concentrations in the CSPA-MD than the PTD regardless of which end of the manufacturer range was used (Table 6). When we added product component to the matching scheme, 16-50% of the combinations had higher concentrations in the PTD compared to the CSPA-MD. For restricted chemicals, the range with higher concentrations in the PTD was 35-77%. There was no appreciable difference in the percentage of product family chemical combinations with lower concentrations in the CSPA-MD compared to the PTD for all chemicals (18%) and contaminants (23%). This indicates that in general, manufacturers reported higher concentrations than what the state is measuring, with the exemption of restricted chemicals.

Table 1- Number of records (individual reports or measurements), unique product family chemical combinations (may contain multiple reports) and the average number of reports within each product family chemical combination

Data Source	CSPA-MD	PTD[a]
Number of Records with Matches	40204	8344 (1606 detects)
Number of Unique Product Family/Chemical Combinations	373	365 (158 detects)
Average number of records within each Product Family Chemical Combination	107.5	13.6
Number of Unique Product Family Component Chemical Combinations	1152	525 (202 detects)
Average number of records within each Product Family Component Chemical Combination	37.8	5.4

[a]141 PTD records were excluded due to QC failure, one PTD product family chemical combination was excluded due to QC failure

Table 2- Concentration ranges reported by manufactures along with the assigned mid-point for the concentration comparison in this analysis

	Range	Assigned Midpoint

Range 1	>PQL ≤100ppm	Dependent on PQL [a]
Range 2	>100ppm and ≤500ppm	300
Range 3	>500ppm and ≤1,000ppm	750
Range 4	>1,000ppm and ≤5,0000ppm	3000
Range 5	>5,000ppm and ≤1,0000ppm	7500
Range 6	>10,0000ppm	185509[b]

[a]The midpoint was calculated using this formula: (PQL+100)/2

[b]The midpoint of the highest range was set to the midpoint of the state data at or above 10,000 ppm

Table 3: Comparison of state measurements by detection with manufacture reports for product family chemical combinations.

	Manufacturer Reports	Manufacturer Non-reports	Percent Reported
State Detects	8	3	73%
State Non-detects	128	19	87%
State Detects and Non-detects[a]	130	77	63%
State Not Tested	107		

[a]For some product family chemical combinations multiple analyses were run on the same combination and the results included both detects and non-detects

Table 4: Comparison of state measurements by detection with manufacturer reports for product family chemical component combinations.

	Manufacturer Reports	Manufacturer Non-reports	Percent Reported
State Detects	24	21	52%
State Non-detects	158	165	48%
State Detects and Non-detects[a]	131	26	80%
State Not Tested	865		

[a]For some product family chemical combinations multiple analyses were run on the same combination and the results included both detects and non-detects

Table 5: The ten product family chemical combinations with the highest over and under reporting rates based on differences between the average of the state measurements and the average of the midpoint from manufacturers ranges.

Ten Chemical-Product Matches with Greatest **Under** Reporting		Ten Chemical-Product Matches with Greatest **Over** Reporting	
Clothing	Cadmium	Baby Welfare	Tetrabromobisphenol A
Arts/Crafts/Needlework Supplies	Diisononyl phthalate	Clothing	Diethyl phthalate
Toys/Games	Diisodecyl phthalate	Toys/Games	Butylparaben
Cosmetics/Fragrances	Diisodecyl phthalate	Personal Accessories	Molybdenum
Footwear	Diisononyl phthalate	Toys/Games	Ethylparaben
Household/Office Furniture	Arsenic	Toys/Games	Diisononyl phthalate
Hair Products	Antimony	Toys/Games	Molybdenum
Arts/Crafts/Needlework Supplies	Diisodecyl phthalate	Toys/Games	Diethyl phthalate
Kitchen Merchandise	Formaldehyde	Arts/Crafts/Needlework Supplies	Molybdenum
Baby Welfare	Tris(2-chloroethyl) phosphate	Arts/Crafts/Needlework Supplies	Antimony

Table 6: Percent of combinations reported in lower concentrations in the CSPA-MD compared to the PTD using the low, midpoint or high end of the manufacturers' reported concentration range.

	Low	Midpoint	High
Product Family Chemical Combinations	31%	18%	16%
Restricted Product Family Chemical Combinations	41%	41%	41%
Product Family Component Combinations	50%	19%	12%
Restricted Product Family Component Combinations	77%	35%	35%

Figure 1. Log mean concentrations for product family chemical combinations reported by manufacturers and detected by Washington State Department of Ecology. The concentration is shown by chemicals (each data point represents a product family) on the right and byproducts (each data point represents a chemical) on the left.

4. **Discussion**

We observe that in general, manufacturers reported higher concentrations of chemicals of high concern to children in children's products than the state measured. This trend fits with the structure of the CSPA regulation which requires manufactures to report the highest concentration of 88 chemicals of high concern to children in children's consumer products found in any product sold or manufactured in Washington State. Additionally, the State has the authority fine manufacturers $5,000-$10,000 per offense for underreporting, however there are no consequences for over-reporting. It is important to note that Ecology's outreach efforts have been successful in facilitating compliance. This structure provides a disincentive for underreporting but has no consequences for over-reporting. Restricted chemicals are less likely to be over-reported. For example, seven of the ten product family chemical combinations most likely to be under-reported are restricted in children's products while only 2 of the ten product family chemical combinations most likely to be under-reported are restricted. Overall, 82% of product-family chemical combinations are over-reported, while only 59% of restricted product-family chemical combinations are over-reported. While there are financial consequences for both under and over reporting restricted chemicals, Ecology also reaches out to manufacturers overreporting restricted chemicals to double check accuracy. This effort is not conducted on unrestricted chemicals. The unevenness of outreach across chemicals may contribute to the differences in over-reporting rates as well as the fee structure.

However, if 82% of the product-family chemical matches are over-reports, it is challenging to use the manufacturers data for prioritization products and chemicals for future action. This highlights the need for the product testing database maintained by the State. Children's product reporting requirements are becoming more common in the US, yet no other states include a publicly available database of chemicals measured in children's products. The Oregon Toxic Free Kids Act has a similar structure to Washington's CSPA, but allows manufactures to report a toxic chemical in a children's product for three cycles of biennial reporting before they need to remove the chemical or pay $1500 and apply for an exemption [20]. Additionally, while the Oregon Toxic Free Kids Act does not require manufactures to report low concentrations (less than 100ppm) of contaminants, manufactures are charged $150 per unique chemical report [20]. This is one example of how the structure of required reporting can be modified as a disincentive to over-report. Once the Oregon data is publicly available, future studies comparing Washington and Oregon reporting rates would contribute to the research supporting the development of regulations that are associated with accurate reporting.

While there are challenges to using the CSPA-MD for chemical prioritization based reported chemical concentration, the functional information reported in the CSPA-MD could be useful for prioritization. The Environmental Protection Agency has recently invested in a database for functional use of chemicals in consumer products based on the premise that integration of chemical toxicity and functional use information can allow for the identification of hazardous chemicals earlier and steer manufacturers towards using safer alternatives [21]. The Functional Use Database builds high-throughput models of quantitative structural use relationships, basing projected function on molecular and chemical properties [21]. While we do not observe any differences in the agreement of the two databases based on function, understanding how chemicals are used in consumer products can allow for prioritization based on the availability of safer alternatives [22]. Chemical function can be used to identify the functional needs for safer alternatives and instances when safer alternatives may be available.

In addition to contributing to our understanding of the efficacy of children's products reporting requirements, we also highlight the need for more comprehensive regulations, as high concentrations of toxic chemicals are found in both the CSPA-MD and the PTD. Particularly concerning are the high concentrations of chemicals measured in children's products designed for personal care that may be applied directly to the skin or body. For example, 14 of the 21 product-family, component, chemical combinations measured in the PTD but not reported in the CSPA-MD, are for personal care/hygiene, hair products, skin products or cosmetics. While most of these chemicals are phthalates and metals, others have reported volatile chemicals in children's hygiene products [23]. The FDA regulates cosmetics through the Food, Drug and Cosmetic Act which prohibits products from bearing or containing ".. any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or under conditions of use as are customary and usual" [24]. However, children are exposed to toxic chemicals in multiple consumer products throughout their lives. Wang et al. 2018 recently identified 669 environmental organic acids in maternal serum [25]. Many of the environmental organic acids identified are derived from consumer product exposures, such as phthalates and phenols. So it follows that, even though exposure to one product may not result in adverse health consequences, the cumulative exposure to these products may impact child health and development.

There are currently gaps in regulation of children's consumer products. One gap is that regulations can vary by jurisdiction. This can contribute to compliance challenges for manufacturers which can be especially prevalent in smaller markets [26]. Another gap, is that the focus on children's products fails to protect pregnant women. Vulnerability to toxic chemicals begins before birth and current children's product regulations fail to capture exposures of pregnant and post-partum women which can impact child health and development. A recent study found that pregnant women are exposed to toxic chemicals through the use of personal care products [27]. Zota et al. 2017 highlight the importance of the indoor environment for exposure to toxic chemicals from consumer product through air and dust [28]. Because people spend approximately 90% of their time indoors [29], reducing indoor exposures can have a substantial impact on total exposures. Behavioral changes and risk communication messaging are not sufficient to reduce exposures, especially for vulnerable populations. Hartman et al. 2017 found that even educated and interested consumers are not able to interpret hazard information [30]. Thus, action is needed at the State and Federal levels to expand regulation of consumer products to protect children throughout development.

4.1 Limitations: This analysis provides an overall comparison of concentrations of chemicals of high concern to children reported by manufactures and measured by Washington State Department of Ecology. However, the datasets have some limitations. The CSPA-MD does not report individual product descriptions, exact concentrations or non-detects. While the PTD provides these details, it is not comprised of a random sample of children's products but is enriched to detect violations.

Differences in the details of products reported means that we are unable to compare identical products. To overcome this challenge, we match by product family, thus each product family group represents the average concentration of a chemical from all products in that family. More granular combinations using the product-class or product-brick levels allows for the comparison of more similar products, but substantially reduces the number of products within each comparison group. When we added the product component to the matching scheme, there

are insufficient matches to complete the analysis using the brick or class level. Using the family level matching allows the product component to be included but means that a wider variety of individual products might be grouped together.

While manufacturers are obligated to report the concentration range of chemicals of high concern to children in any children's product sold or manufactured in Washington State, products included in the PTD are selected for outreach and potential enforcement. This means that the PTD is not a random sample. Restricted chemicals are measured more frequently and products more likely to contain higher concentrations of chemicals of high concern to children are tested more frequently. As such, we would expect it to generally contain higher concentrations of chemicals and higher detection rates. Our observation that the PTD generally has lower concentrations than the CSPA-MD contrasts with the expected implication of non-random sampling within the PTD.

The CSPA-MD reports concentrations in ranges instead of point values. Since the ranges can be quite large and are not related to chemical potency, it is challenging to compare them to point values measured in the PTD. In order to understand how the ranges contributed to variability in misclassification, we use the low, midpoint and high end of the range in our comparison. We find that between 16%-50% of product-family, component, chemical combinations are under-reported. This range is significant and further refinement of the ranges manufacturers report within would improve our ability to characterize the differences between the databases.

4.2 Conclusions: In general, we observe that the CSPA-MD has higher concentrations of chemicals of high concern to children than the PTD. When we pull out chemicals with concentration limits in children's products, we find that the percentage of product-family component chemical combinations that are higher in the PTD than the CSPA-MD increases from 19% to 35%. This suggests that restricted chemicals may be less likely to be over-reported.

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Supplemental Information for Chapter 2:

Table S1: Product chemical combinations by product, family, class and brick in the CSPA-MD and the PTD

Matching Level and Description		CSPA-MD	PTD
Product Family/Chemical	Number of unique combinations	373	365
	Average number of records within each combination	107.5	13.6
Product Class/Chemical	Number of unique combinations	971	768
	Average number of records within each combination	36.3	10.2
Product Brick/Chemical	Number of unique combinations	2533	1775
	Average number of records within each combination	13.9	4.4

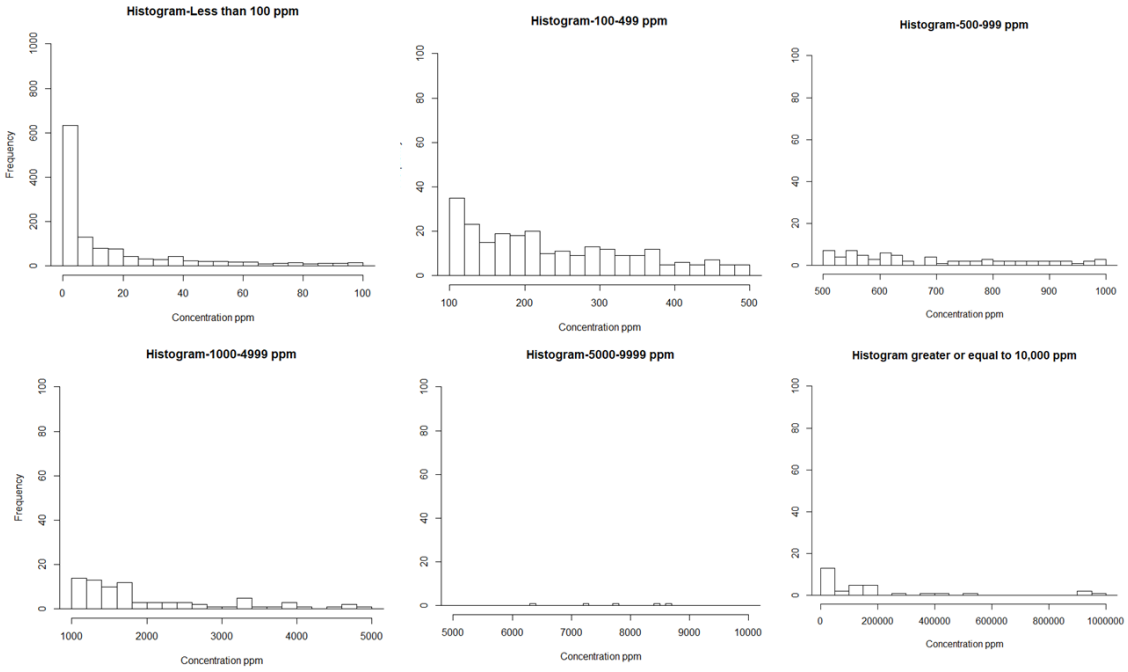
Table S2: Product-family component chemical combinations detected in all state measurements but not reported by manufacturers and relevant regulations.

Family	Chemical	Component	Average PTD Concentration	Number of records
Beauty/Personal Care/Hygiene Variety Packs	Cadmium	Synthetic Polymers (synthetic rubber, plastics, foams etc	255	2
Cosmetics/ Fragrances	Antimony	Textiles (synthetic fibers and blends)	197	1
Hair Products	Antimony	Metals (Including alloys)	6.2	1
Hair Products	Arsenic	Metals (Including alloys)	122	1
Hair Products	Arsenic	Synthetic Polymers (synthetic rubber, plastics, foams etc.)	9.16	1
Hair Products	Cadmium	Synthetic Polymers (synthetic rubber, plastics, foams etc.)	5.4	1

Hair Products	Cobalt	Synthetic Polymers (synthetic rubber, plastics, foams etc.)	1.9	1
Hair Products	Mercury	Synthetic Polymers (synthetic rubber, plastics, foams etc.)	0.082	1
Hair Products	Molybdenum	Metals (Including alloys)	37.9	1
Household/Office Furniture	Antimony	Metals (Including alloys)	1.87	1
Household/Office Furniture	Arsenic	Metals (Including alloys)	2770	1
Household/Office Furniture	Cobalt	Metals (Including alloys)	262	1
Household/Office Furniture	Molybdenum	Metals (Including alloys)	15.5	1
Kitchen Merchandise	Cobalt	Glass, Ceramic and Siliceous material	61.5	3
Personal Accessories	Cadmium	Glass, Ceramic and Siliceous material	1.7	1
Personal Hygiene Products	Diethyl phthalate	Homogenous Mixtures (gels, creams, powders, liquids, adhesives, synthetic fragrances)	1500	1
Skin Products	Antimony	Metals (Including alloys)	2.7	1
Skin Products	Arsenic	Metals (Including alloys)	61	1
Skin Products	Cobalt	Metals (Including alloys)	25	1
Skin Products	Molybdenum	Metals (Including alloys)	3.8	1
Stationery/Office Machinery	Cadmium	Synthetic Polymers (synthetic rubber, plastics, foams etc	2.0	2

*Molybdenum was removed from the required reporting list in 2017

Figure S1: Histograms of the concentrations PTD measurements within the CSPA-MD concentration ranges.


Histogram-Less than 100 ppm
Frequency
Concentration ppm
Histogram-100-499 ppm
Concentration ppm
Histogram-500-999 ppm
Concentration ppm
Histogram-1000-4999 ppm
Frequency
Concentration ppm
Histogram-5000-9999 ppm
Concentration ppm
Histogram greater or equal to 10,000 ppm
Concentration ppm

CHAPTER 3:

Title: A Case study on the utility of predictive toxicology tools in alternatives assessments for hazardous chemicals in children's consumer products

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Abstract:

Children's consumer products represent an important exposure source for many toxicants. Chemicals of high concern, as designated by the Washington State Child Safe Product Act include phthalates, Bisphenol A (BPA) and parabens, among others. As regulation and reporting requirements increase, so has demand for safer alternatives. This project examines how predictive toxicology and exposure comparison tools can fill gaps in alternatives assessments for hazardous chemicals found in children's products. Phthalates, parabens, BPA and their alternatives were assessed for endocrine disruption and reproductive toxicity using authoritative lists and US Environmental Protection Agency's (EPA) predictive toxicology and exposure comparison tools. Resources included the European Chemical Agency's Endocrine Disruptor Substances of Concern database, Global Harmonization System and Classification of Labeling Chemicals, Quantitative Structural Activity Relationships from the Toxicity Estimation Software Tool, the Toxicological Prioritization Index (ToxPi) score calculated from the ToxCast Database, and No Observable Adverse Effects Levels (NOAELs)/Highest No Effects Levels (HNEL) from animal studies found in the CompTox Chemistry Dashboard. Exposure was assessed using ExpoCast predictions. Though alternatives were rarely included in authoritative lists, predictive toxicology tools suggested that BPA alternatives may not be safer but paraben and phthalate alternatives may be safer. All four paraben and no bisphenol or phthalate alternatives were listed on EPA's Safer Chemical Ingredients List. Overall, we found that predictive toxicology tools help fill gaps for alternatives assessments when existing classifications are incomplete.

Keywords: Children's Health, Consumer Products, Alternatives Assessment, Endocrine Disruption

Introduction

One of the principles of green chemistry is to design safer chemicals considering potential health and ecological hazards from creation through disposal[1]. Safer chemical substitutions are often identified by alternatives assessments. Guidance or review documents on alternatives assessments have been released by the National Academy of Sciences (NAS) [2], Interstate Chemical Clearinghouse [3], the U.S. Environmental Protection Agency (EPA) [4] and the Organisation for Economic Co-operation and Development[5]. Like many guidance frameworks, the NAS begins with the identification of hazardous chemicals and then screens for whether alternatives are available. If alternatives are available, they are screened for chemical and physical properties, human health and ecological hazards. Most human health assessments follow the hazard identification step in the traditional risk assessment framework [6]. The NAS suggests the inclusion of in vitro data to fill data gaps when human and animal data are not available. This call was reiterated in Tickner et al. 2018, with a push to advance the use of predictive toxicology tools for filling data gaps in alternatives assessments [7].

In addition to exposure comparison, consideration of function, analysis of economic feasibility and lifecycle assessment, alternatives analyses require the full hazard assessment of at least two chemicals, increasing the likelihood of data gaps, especially for newer chemicals. Lack of data is not an indication of safety and approaches to bridge data gaps are highly important for alternatives assessments. Regrettable substitutions, such as the replacement of methylene chloride with n-hexane in brake fluid can be counter-productive to the overall goals of green chemistry and alternatives assessments.

This paper focuses on three chemical groups of high concern to children with members among the 85 chemicals designated by the Washington State Children's Safe Product Act (CSPA): Bisphenol A (BPA), Phthalates and Parabens. BPA is used as a coating for plastic consumer products, such as water bottles, food storage containers and electronics. While BPA has not been banned in the United States, the Food and Drug Administration (FDA) has restricted BPA concentrations in baby bottles, sippy cups and some food packaging due to its endocrine disrupting capability and reproductive and developmental toxicity [8]. Low dose exposures can be particularly damaging during sensitive periods of development [9]. Despite the lack of more extensive regulation from the Consumer Product Safety Commission and the FDA, consumer concern has driven the development of BPA-free products. Many of these products contain bisphenol-S (BPS) as a replacement compound. While some assessments have found BPS to be safe in children's products [10], others find that BPS has similar toxicological attributes as BPA [11,12].

Phthalates are plasticizers found in a wide array of consumer products. Concerns over exposures to phthalates in consumer products have led to regulations at the state and federal level in the United States. The US Consumer Product Safety Improvement Act (CPSIA) of 2008 limits the use of some hazardous chemicals, including six phthalates, lead and cadmium in children's products [13]. Three phthalates; DEHP, DBP, and BBP concentrations are restricted to no more than 1000 ppm per individual phthalate in children's toys and products designed to care for children under age three. DINP, DIOP and DnOP are restricted in concentrations greater than 1000 ppm per individual phthalate in children's toys that can be placed in a child's mouth and in products designed for care of children under age three. These and other state regulations, such as CSPA, passed in 2008 in Washington State, which limits the total concentration of phthalates in any child's product to 1000 ppm [14], are pushing industry to identify alternatives for phthalates. While the majority of regulations are focused on children's products, some companies have voluntarily removed phthalates from their products. Apple removed phthalates from cords and headphones in 2013 and Lowe's Home Improvement and Home Depot quit selling vinyl flooring that contains phthalates in 2015 [15]. While some manufacturers are working to completely remove phthalates, others have begun using less toxic phthalates. For example, manufacturers are using DINP instead of DEHP because DINP has a lower toxicity and a higher molecular weight, making it less likely to migrate out of plastics [15]. Phthalate alternatives are less publicized than the alternatives to BPA however, the Lowell Center for Sustainable Production at the University of Massachusetts developed a technical briefing to identify these compounds [16].

While there have been no limits on parabens in children's consumer products, there is a consumer-led initiative for paraben free products. A recent guide for pediatricians regarding endocrine disrupting chemicals suggested avoiding personal care products that contained parabens because in vitro studies have found estrogenic and anti-androgenic potential [17]. Parabens are incorporated into consumer products as preservatives. Thus, it is important to determine which preservatives are replacing parabens and whether these compounds are less toxic.

This case study of BPA, parabens and phthalates will help to determine whether predictive tools (in vitro and in silico models) can fill data gaps in exposure and toxicity assessment of alternative and conventional chemicals found in children's consumer products. We hypothesize

that predictive exposure and toxicology tools will allow us to better characterize the hazard and potential exposures of alternative chemicals. As regulations of chemicals in children's consumer products are becoming more common, it is important to identify sources of data for determining whether the alternative chemicals are in fact safer.

Methods:

Three case studies were investigated: BPA, phthalates, parabens. For each of these case studies, the relevant substitution chemicals were identified and hazard was assessed for endocrine disruption and reproductive and developmental toxicity. Hazard was characterized using authoritative lists and predictive toxicology tools. Exposure comparisons were made using an in silico predictive exposure model. Figure 1 shows the integration of the various hazard and exposure assessments and data levels.

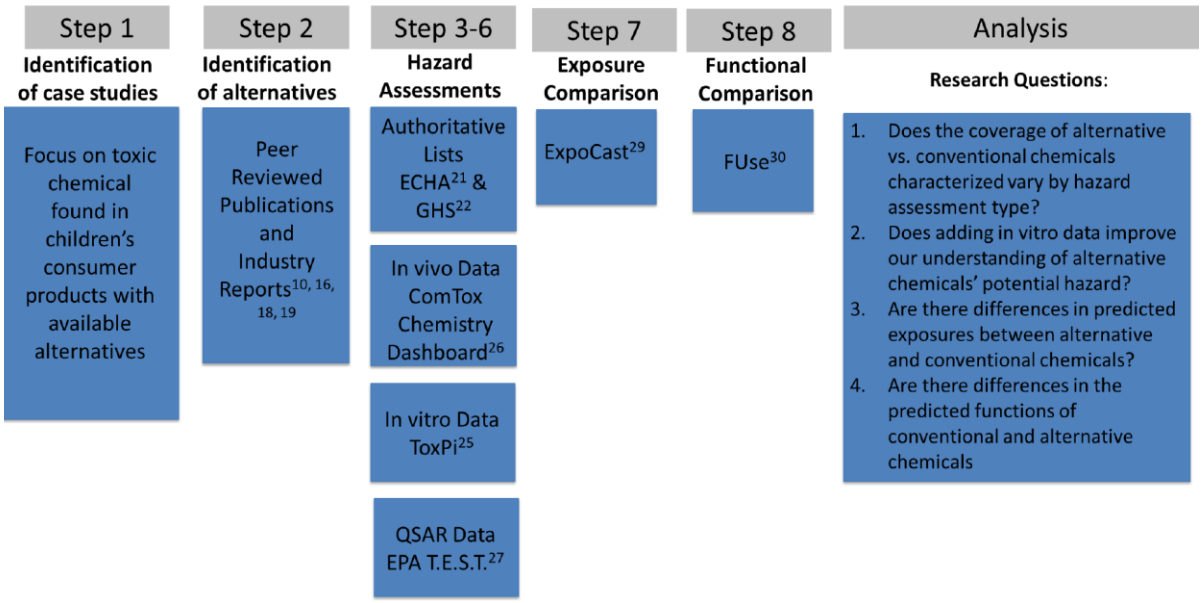

Figure 1: The steps used to identify case studies, alternatives and integrate hazard assessments from multiple data levels.

Step 1 and 2: Identification of case studies and alternatives: Case studies were identified based on the following criteria: 1. these groups (among others) are reported under CSPA in Washington State 2. there are children's products marketed as being free of these chemicals and 3. there is evidence of toxicity. We conducted a review of reports and peer reviewed literature to identify publications containing alternatives to the case study chemical groups [18,19] [10] [16]. We used the search terminology: "chemical group" "alternatives" and "consumer products" in PubMed and Google Scholar to identify articles. We reviewed papers looking specifically for alternative chemicals already in use, not proposed or potential alternatives. This case study did not attempt to identify all potential alternatives to conventional chemicals. Instead, we focused on a narrow group of alternatives as a "proof of principle" for the use of in vitro and in silico tools for filling data gaps. Conventional and alternative compounds are provided in Table S1.The alternatives were compared with the EPA's Safer Choice Program's Safer Chemical Ingredients List (SCIL) [20]. This list is designed to help manufacturers choose safer chemicals for use in their products and ingredients. Chemicals on the list are grouped by function and classified according to criteria for human health, environmental toxicity and environmental fate. The classification is based on experimental and modeled data.

Step 3: Hazard Characterization- Authoritative lists

Authoritative lists are screening tools developed to aid regulatory agencies in chemical prioritization. As such, they are not exhaustive or comprehensive, yet they frequently serve as a

starting place for toxicity assessment. Endocrine disruption and reproductive toxicity was based on the European Chemicals Agency (ECHA) Endocrine Disruptor Substances of Concern database[21]. This list is designed to prioritize chemicals for further assessment. Substances are categorized from 1-3. Category 1 includes known endocrine disruptors while categories 2 and 3 include suspected endocrine disruptors. We also included chemicals listed as reproductive toxicants in the Global Harmonization System (GHS) [22]. While there are differences in endocrine and reproductive toxicity mechanisms, the in vitro assays considered in this analysis have been used for both endocrine and reproductive toxicity assessment[23]. The GHS aims to internationally harmonize the classification and labeling of chemicals. Reproductive toxicity is categorized into three groups: 1A (known reproductive toxicity based on human data), 1B (presumed reproductive toxicity based on experimental animal data) and 2 (suspected reproductive toxicity based on human or animal evidence possibly with other information).

For data analysis purposes, if a chemical was included in either of these sources, it was considered to be present on an authoritative list. The categorizations from both of these lists are shown in Table S1.

Step 4: Hazard Characterization- in vitro

ToxCast is a high throughput toxicity screening program that uses 821 assay endpoints assessed using in vitro assays from human and animal cell lines as well as cell free assays. ToxPi is a prioritization support software tool [24] that uses in vitro assay data from ToxCast, physicochemical properties, and toxicity pathways to identify potential endocrine disrupting chemicals by considering their responses across a variety of endocrine disrupting assays, including estrogen, androgen, thyroid, glucocorticoid and PPAR disruption [25]. Data from ToxCast is combined with the logarithm of the water octanol partition coefficient and the bioconcentration factor to develop a score[25]. ToxPi scores are normalized for cytotoxicity. Scores fall between zero and one with higher scores indicating higher endocrine disruption potential. ToxPi scores for chemicals and alternatives were accessed from those published in Filer et al. 2014 [25] and reflect the prioritization based on 1858 chemicals. A full list of ToxPi Scores is shown in Table S1.

Step 5: Hazard Characterization- in vivo

The EPA's CompTox Chemistry Dashboard (https://comptox.epa.gov/dashboard)[26] was used to access animal data from ECHA and EPA sources including: COSmetics to Optimise Safety (COSMOS http://www.cosmostox.eu/what/databases/) , ToxRefDb, Tox21, High Production Volume Information System (HPVIS), Integrated Risk Information System (IRIS), Hazard Evaluation Support System Integrated Platform (HESS) and others. The No Observable Adverse Effects Level (NOAEL) or Highest No Effects Level (HNEL) was used to assess the hazard from in vivo studies. The NOAEL or HNEL from the CompTox Chemistry Dashboard was used to compare the relative hazard between conventional and alternative chemicals. To be protective, the lowest NOAEL from a rodent study with oral exposure was used. Oral exposure was selected because it was the most common and relevant exposure route assessed, and as such it allowed for the most consistent comparison across chemicals. For some chemicals, only the Lowest Observable Adverse Effects Level (LOAEL) or Lowest Effects Level (LEL) was available. In this case, it was converted to a NOAEL by dividing by an uncertainty factor of 10. The studies used followed a repeat exposure framework, with some studies including prenatal or multigenerational dosing structures.

Step 6: Hazard Characterization- Quantitative Structural Activity Relationships

Characterization of unknown chemicals frequently begins with looking at the molecular structure and comparing its features with known toxicants. The EPA Toxicity Estimation Software Tool (T.E.S.T.) can characterize the toxicity of unknown compounds using Quantitative Structural Activity Relationships (QSAR)[27]. We used T.E.S.T. version 4.2 to predict the developmental toxicity of conventional and alternatives chemicals. T.E.S.T. uses 797 2-

dimmensional molecular structure descriptors, such as the number of benzene rings to predict toxicity. We set T.E.S.T to run using the consensus model, which combines results from four models (singular, hierarchical, FDA and nearest neighbor) and has been shown to generate the best results for screening with higher sensitivity than specificity. The formulas for these models is available in the T.E.S.T. manual[27]. In this case, developmental toxicity was defined as a binary variable that includes any effect interfering with normal development before or after birth. The binary toxicity valued were developed by the CESAR Project [28]. The model is based on experimental data from the Teratogen Information System and the Food and Drug Administration and consists of 285 chemicals[28].

Step 7: Comparative Exposure Prediction- in silico

Exposure comparison is an important step in alternatives assessment[2]. It can be challenging to find exposure data for both conventional and alternative chemicals. Prediction of exposure is important for chemicals in children's consumer products as children have a high frequency of hand to mouth activity. The ExpoCast initiative by the EPA aims to create tools for screening the thousands of chemicals that are relevant for human exposure. Chemical use information and fate and transport models are used to estimate exposure. Chemical release information for ExpoCast is derived from production volumes found in the EPA Chemical Data Reporting Rule (previously called the Inventory Update Reporting Rule). From this information ExpoCast generates an estimated exposure for 1936 ToxCast chemicals with sufficient information. Exposure predictions in mg/kg/day from Wambaugh et al. 2014 for children age 6-11[29] were used for this analysis and are shown in Table S1.

Step 8: Function Prediction- in silico

Because alternatives assessments aim to determine whether there is a safer alternative, it requires the assessor to consider functionality [2]. Phillips et al. 2017 developed quantitative structural use relationship (QSUR) models and the Functional Use (FUse) Database to classify the function of chemicals found in consumer products [30]. QSUR models can help relate physiochemical properties with how chemicals are used in consumer products. In this analysis we compared the functions of conventional and alternative chemicals. EPA's FUse Database provides functional use predictions for approximately 6400 chemicals. The Fuse Database was accessed through the CompTox Chemistry Dashboard. The Harmonized Functional Use category with the highest predicted probability for use for each chemical was assessed to compare functional use between conventional and alternative chemicals.

Data Analysis: ToxPi scores, NOAELs and ExpoCast exposure predictions were compared using the average of each chemical group and the standard error. QSAR data was binary and the percent of chemicals within each group that are predicted developmental toxicants was calculated using only chemicals found in the EPA T.E.S.T. database. Because this is a case study and some chemical groups only contained 1 chemical, it was not appropriate to do statistical analyses. In order to compare functional use, the average of the highest predicted probability for harmonized functional use category for each chemical group (alternative vs. conventional) was calculated. We used a ratio approach to determine how hypothetical changes in efficacy, and therefore exposure, might impact public health. For the example of parabens, we calculated the ratio of the ToxPi scores for conventional/alternative chemicals. If this ratio is over one, then the alternatives are less toxic. However, to achieve the same function as the conventional chemical, an alternative might be added at higher concentrations. We chose to only do this analysis for parabens, as the ToxPi Scores for alternative and conventional bisphenols and phthalates shared the same standard error range.

Results

Assessment of Coverage of Conventional and Alternative Chemicals:

Overall, conventional chemicals were more likely included in the list of endocrine disruptors published by ECHA and GHS than alternative chemicals for all three chemical groups

(phthalates, parabens and bisphenols). Data from in vivo animal studies improved coverage for alternative chemicals for bisphenols and phthalates, but not for parabens. In vitro data improved coverage for all three chemical groups. Except for paraben alternatives, QSAR data had the greatest coverage of all data types. Table 1 shows the number of conventional chemicals and alternative chemicals found in authoritative lists, in vivo, in vitro and QSAR databases for each of the three chemical groups.

The in vivo studies selected for this paper are described in Tables S1 and S2. While conventional chemical studies frequently focused on specific endpoints, such as endocrine disruption or reproductive and developmental toxicity, alternative chemicals were more likely to have non-specific endpoints. NOAELs and study references are shown in Table S1.

Table 1: Number chemicals and percentage within each chemical group included in authoritative lists, animal in vivo databases, in vitro databases and QSAR tools for endocrine disruptions or reproductive and developmental toxicity.

Conventional Chemicals Coverage				
Chemical Group	Lists (ECHA & GHS) % (n)	in vivo % (n)	In vitro % (n)	QSAR % (n)
Bisphenols (n=1) BPA	100% (1)	100% (1)	100% (1)	100% (1)
Parabens (n=4) Methyl, ethyl, propyl and butyl parabens	50% (2)	75% (3)	100% (4)	100% (4)
Phthalates (n=9) DnOP, DIDP, DINP, DnHP, DEHP, DEP, DBP, BBP	89% (8)	78% (7)	67% (6)	100(9)
Alternative Chemicals Coverage				
Bisphenols (n=2) BPS, BPF	0 (0)	100% (2)	100% (2)	100% (2)
Parabens (n=4) Benzoic acid, Potassium sorbate, Sodium benzoate, Sorbic acid	25% (1)	100% (4)	75% (3)	50% (4)
Phthalates (n=17) Aceyl tributyl citrate, Di-isononyl-cyclohexane-1, 2 dicarboxylate, dioctyl terephthalate, epoxidized soybean oil, alkylsubphonic phenyl ester, tri-2-ethylhexyl trimellitate, acetylated monoglycerides of fully hydrogenated caster oil, 4-benzenedicarboxylate, di-butyl adipate, butylated hydroxytolulene, hyper branched poly, di (2 ethylhexyl) phosphate, tri (2ethylhexyl) phosphate, o-tolulene sulfonamide, 2,2,4 trimethyl 1,3 pentanediol diisobutyrate, diocytl sebate , dibutyl sebate, di (2- ethyl hexyl adipate)	18% (3)	59% (10)	82% (14)	88% (15)

Prioritization Comparison

Authoritative Lists Hazard Characterization: No alternative chemicals were classified as endocrine disruptors ECHA but three were classified as reproductive toxicants by GHS (Table 1, detailed classifications in Table S1). Benzoic Acid (paraben alternative) is classified as a suspected reproductive toxicant by GHS. Ethyl and butyl parabens are both considered endocrine disruptors by ECHA. Di-butyl adipate and butylated hydroxytolulene (phthalate alternatives) are both considered suspected reproductive toxicants by GHS. Eight out of nine of

the phthalates considered in this paper were considered known or suspected reproductive toxicants by GHS as well as known or suspected endocrine disruptors by ECHA.

In vitro Hazard Characterization: Figure 2 shows the average ToxPi score for conventional and alternative chemicals within each chemical group. For phthalates and bisphenols, the average ToxPi score for conventional chemicals was within the standard error range of the alternatives' ToxPi score. For parabens, average conventional ToxPi score was above the standard error range of the alternatives' ToxPi scores.

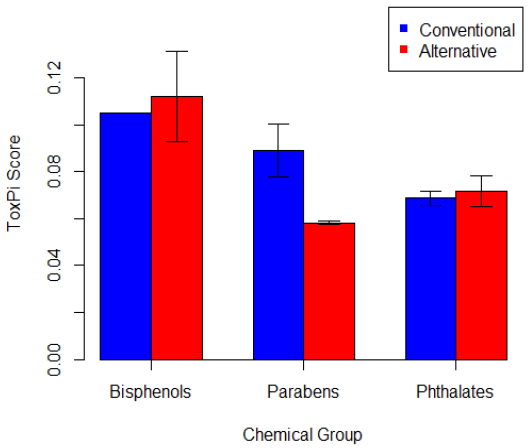

Figure 2: Comparison of the average ToxPi score for conventional and alternative chemicals. Error bars represent standard error. Chemical groups without error bars had an N of 1.

In vivo Hazard Characterization: Animal studies from the CompTox Chemistry Dashboard were used to identify the NOAEL for each chemical (shown in Tables S1 and S2). Of the databases accessed through the CompTox Chemistry Dashboard the majority of the studies came from HPVIS, ECHA and COSMOS. The standard error ranges for NOAELs for phthalates and parabens and their alternative chemicals overlapped, suggesting little difference in toxicity (Figure 3). BPA's NOAEL was lower than the standard error range of its alternatives' NOAELs. However, the NOAEL for BPA was based on developmental neurotoxicity and similarly sensitive endpoints were not available for BPF and BPS. The NOAEL range for paraben and their alternatives were similar. The types of studies used to derive NOAELs are described in Table S2.

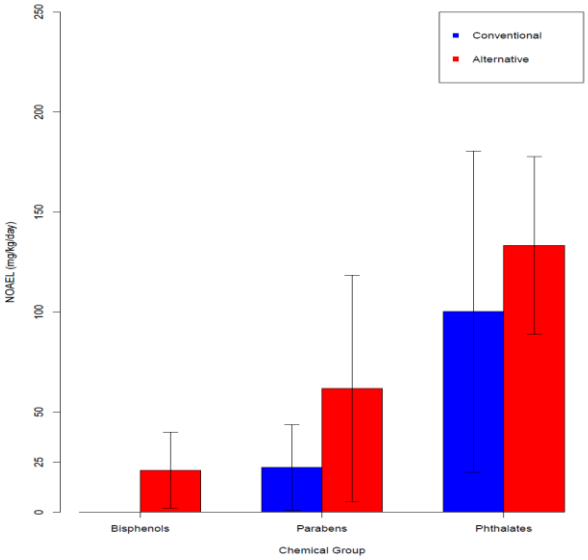

Figure 3: Average NOAELs for conventional and alternative chemicals. Error Bars represent standard error. Chemical groups without error bars had an N of 1.

QSAR Hazard Characterization: Conventional chemicals were more likely to be predicted as developmental toxicants. All conventional and alternative bisphenols were predicted as developmental toxicants. Seventy-five percent of conventional parabens and 50% of alternative parabens were predicted developmental toxicants. Conventional and alternative phthalates were predicted to be developmental toxicants at similar rates, 56% for conventional and 47% for alternative.

In silico exposure comparison: The median exposure predictions for children age six to eleven are shown in Figure 4 and listed in Table S1. The median was used in the comparison, however for most chemicals there is a wide predicted range. For example, BPA has a median exposure prediction of 0.629E-05 mg/kg/day while the 95th percentile is predicted to be 4.98 X 10^{-3}mg/kg/day for children age 6-11. For bisphenols and phthalates, conventional chemicals had higher predicted exposure than alternative chemicals for children age 6-11 (Figure 4). Parabens alternatives had predicted exposure within the standard error range of conventional parabens, suggesting similar exposures (Figure 4).

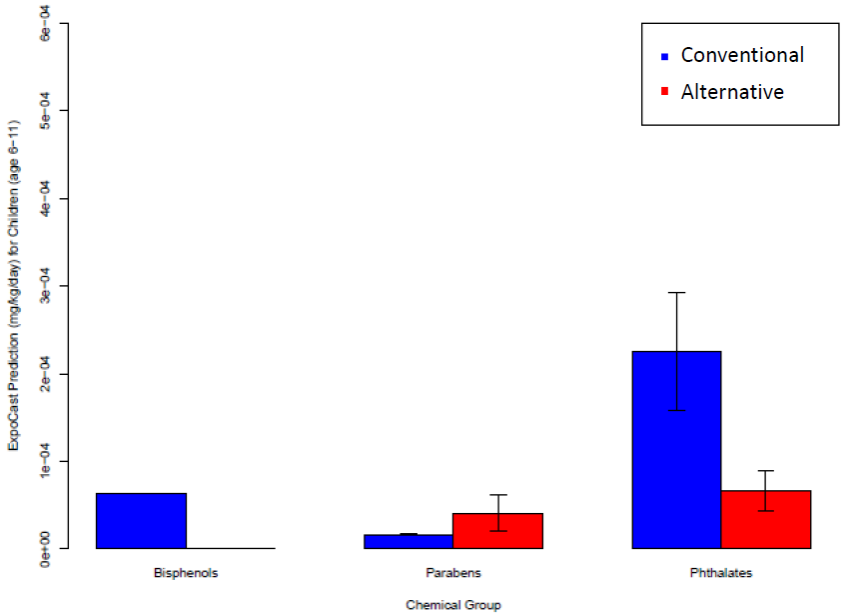

Figure 4: The average ExpoCast prediction for alternative and conventional chemicals for bisphenols, parabens and phthalates. Error Bars represent standard error. Chemical groups without error bars had an N of 1.

Functional Prediction: The harmonized functional use categories with the highest probabilities for alternative and conventional chemicals are shown in Figure 5. There was more diversity in the functional category with the highest predicted probability among alternative chemicals for bisphenols and phthalates. Parabens and their alternatives were both most likely to be found in preservatives.

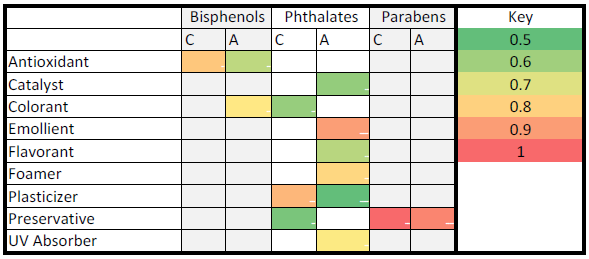

Figure 5: Harmonized Functional Use Categories from the Fuse Database accessed from the CompTox Chemistry Dashboard for Alternative (A) and Conventional (C) Chemicals. Colors represent the average of the highest predicted probabilities for each chemical group by functional use category. As is shown in the key, red indicates a higher probable function and green indicates a lower probably function.

Selecting Safer Alternatives:

The alternative chemicals identified for this case study were compared with SCIL. None of the phthalate or BPA alternatives were listed on the SCIL, but all four of the paraben alternatives were on SCIL. All the alternatives included in SCIL were classified as a "green circle" meaning the "chemical has been verified to be of low concern based on experimental and modeled data." This allows us to put the toxicity results shown in Figures 2 and 3 in the context of recommended alternatives. For example, BPS and BPF, the primary BPA alternatives, are not listed as safer chemicals on SCIL and have been identified as potential regrettable substitutions. This is supported by multiple reports in the peer reviewed literature of BPS and BPF having similar toxicity to BPA [11,12]. The replacement of BPA with BPS and BPF is considered a regrettable substitution. BPF and BPS were not listed on any of the authoritative lists consulted. While the NOAEL for BPA was lower than the standard error ranges for NOAELs of BPA alternatives, the ToxPi scores suggested little difference in toxicity. The NOAEL for BPA is based on developmental neurotoxicity, a highly sensitive endpoint. Developmental neurotoxicity NOAELs were not available for BPF and BPS. The discrepancy in sensitivity of endpoints might account for the observed different in NOAELs between BPA and its alternatives. All four of the alternative paraben chemicals were listed on SCIL. While these chemicals were not included in authoritative lists, the average NOAEL was higher and the average ToxPi score was lower than for parabens, indicating safer options. The results from this analysis are congruous with SCIL.

When considering safer alternatives, it is important to determine whether a higher concentration of the alternative chemical may be needed to achieve the same efficacy. A simple approach to estimate how an increase in the concentration of alternative chemicals, relative to conventional chemicals might affect public health impact is to consider the ratio of the conventional and alternative toxicities. In this case study, we used the ToxPi scores for parabens and their alternatives. Because the ToxPi scores for conventional and alternative phthalates and bisphenols had overlapping standard error ranges, the ratio would be about one and is not informative. The ratio of conventional to alternative paraben ToxPi scores was 1.54 (Table 2). Even if the alternative is half as effective and the concentration has to be increased, it may still lead to a positive public health impact.

Table 2: Integrating exposure potential and toxicity considerations: the ratio of the average conventional/alternative chemical ToxPi Scores.

	Compound	ToxPi Score	Group Average +/- Standard Deviation	Ratio of Conventional/ Alternative Averages

Conventional	Methyl Paraben	0.061	0.089+/-0.023	1
	Ethyl Paraben	0.080		
	Propyl Paraben	0.106		
	Butyl Paraben	0.110		
Alternative	Benzoic Acid	0.057	0.058+/-0.0012	1.54
	Sodium Benzoate	0.060		
	Sorbic Acid	0.057		

Discussion:

This work shows that in vitro, QSAR and in silico data sources can provide information about hazard and exposure for chemicals in children's consumer products when authoritative lists are unavailable. These data sources are particularly useful for conducting alternatives assessments as some alternatives may be newer chemicals with less information available. The need for data sources to complete toxicological and exposure comparisons in alternatives assessment was noted in the 2014 National Academy Report "A Framework to Guide Selection of Chemical Alternatives"[2]. This report suggested the inclusion of in vitro data to fill gaps where animal and human data were missing. This concept was elaborated on in a recent analysis of the role of predictive toxicology in alternatives assessment [31]. Malloy et al. 2017 reported that there are "significant gaps in toxicity information for the vast majority of chemicals and exposure pathways" and that this problem is exacerbated in alternatives analysis when often multiple chemicals need to be compared [31]. In addition, Malloy et al. 2017 made four recommendations for integrating and improving alternatives assessment using predictive toxicology. The recommendations included using case studies as examples, using predictive toxicology tools as screening methods, drawing on existing resources to integrate predictive toxicology in alternatives assessments and supporting interdisciplinary collaborations [31]. In this work, we use children's consumer products as a case study for integrating predictive toxicology tools, such as in vitro and in silico data, in alternatives assessments. Jacobs et al. 2016 conducted an extensive review of existing alternatives assessment frameworks [32] and found that exposure assessment was a critical area with missing information. By using existing data and publicly available resources for both exposure and toxicity [33], we were able to show that predictive toxicology tools not only add to the data available for alternatives assessments, but also fill in key gaps when no animal or human studies are available.

This case study suggests that some alternative chemicals may still be hazardous to children's health. While few alternatives were found on authoritative lists, there was overlap in the toxicities of conventional and alternative chemicals using in vivo data, ToxPi and QSAR tools. The ToxPi Scores and QSAR predictions for alternative chemicals were similar to conventional chemicals for bisphenols. Phthalates and their alternatives had similar toxicities in vivo, ToxPi Scores and QSAR predictions. Parabens, had ToxPi scores, but similar in vivo toxicity. This suggests that these alternative chemicals may have similar endocrine disruption activities to the chemicals they are replacing, despite alternative chemicals being included in authoritative lists. Other studies have suggested that bisphenol A alternatives may not be safer [12]. The results of this case study rely on the identification of chemical alternatives as well as information about the associated exposure and toxicity. One limitation to this case study was

the availability of alternatives in use. As more states and governing bodies begin to require toxic chemical reporting, it may be easier to identify alternatives. Having limited access to alternatives in use may impact the results of this case study. However, the additional toxicity, exposure and functional assessment information provides a proof of principle for the utility of predictive toxicology tools for alternatives assessment.

Case studies with alternatives listed on EPA's Safer Chemical Ingredient List, had lower ToxPi Scores and higher NOAELs. All four paraben alternatives were on the SCIL. The ToxPi scores and NOAELs reflect this with paraben alternatives showing lower ToxPi scores and higher NOAELs, relative to parabens. BPA and Phthalate alternatives were not found on the SCIL and did not show this trend in vitro. For parabens, the average ToxPi score was 0.89, compared with 0.58 for alternatives. We used the ratio of these two numbers to begin to account for the impact of changes in concentration or exposure between conventional and alternative chemicals. For example, if alternative chemicals are 65% less toxic, then we might tolerate an increase in concentration and exposure potential, while still protecting public health.

The need for data to support alternatives assessments, particularly for children's consumer products will increase as more states are developing regulations and reporting frameworks. Oregon, Maine, Minnesota and California are all in various stages of implementing laws similar to Washington, increasing industry's interest in tools that support safer alternatives assessment, identification and evaluation of both hazard and exposure. One of the challenges to using alternatives assessments in decision-making is dealing with uncertainty in terms of missing data[34]. Resources are needed to not only address data gaps but also manage the uncertainty associated with incorporating new data streams. As demonstrated in this paper, predictive toxicology and comparative exposure tools can help fill data gaps. In vitro and in silico data, however, have different limitations and tools are needed to understand how to appropriately address these factors. Many State and federal agencies use GreenScreen® for chemical hazard assessment [35]. GreenScreen® is a chemical hazard assessment approach that provides users with guidance on integrating multiple data sources. While in vitro databases are included in the GreenScreen® lists of recommended resources, there is little guidance on how to interpret and include in vitro data. The methods used in this paper, provide an example of how in vitro data can be can help characterize uncertainty and be useful for managing data gaps in chemical hazard characterization for alternatives assessments.

This manuscript is the first case study to examine the utility of predictive toxicology and exposure comparison tools for alternatives assessments for chemicals in children's products. While the applications and conclusions provide a useful platform for identifying future directions and data needs, there are some challenges. For example, information on new chemicals in children's consumer products is hard to find. Additionally, it would be helpful to know how tightly the chemicals are bound to the children's product. While most of the conventional chemicals, especially phthalates, have well-characterized metabolism pathways, information on alternative chemical metabolism in children would add to our assessments, as children can have differences in enzyme expression[34]. Because this study focused on endocrine disruption, chemicals with other mechanisms of toxicity might appear less toxic. It is important to assess all types of toxicity when considering an alternative because it would be regrettable to replace an endocrine disruptor with a carcinogen, for example. One of the benefits of ToxCast is availability of assay data for other endpoints, such as reproductive[35] and developmental toxicity[23] and neurotoxicity[35]. In vitro databases, such as ToxCast can help understand the range of molecular initiating events that are often not studied in a single in vivo study. Other factors that are important for prioritizing alternatives in children's consumer products are listed in Table 3.

Table 3: Information needed to assess toxicity and exposure of alternative chemicals in children's consumer products

Alternative Chemical Properties	Exposure- Product Properties	Toxicity Properties
What alternatives are currently being used? What is the toxicity of the alternatives (in vitro and in vivo)? What are the biokinetic properties of the alternatives? What are the physiochemical properties of the alternatives (QSAR)? Does this alternative have another use/multiple uses? How effective is the alternative? Can it be effective at a similar concentration range or is more needed?	How tightly is the chemical bound to the product? Is there a difference in the bond between alternative and conventional chemicals? How is the product used and misused? How might product use and misuse change exposure potential? What is the intended age range for this product? What happens to the product after its use (fate and transport)? Does the chemical stay bound to the product? Is the chemical stable? What is the concentration of the chemical in the product? What part of the product is the chemical found in? Is it accessible during normal use and misuse?	What is the timing and dosing structure of in vitro toxicity assessments and how does it related to in vivo development? Are the acute and chronic effects different? How might effects be different during development? What is the specificity of the in vivo toxicity assessments conducted? Is the in vivo toxicity assessment focused on a specific and sensitive endpoint? What was the dosing structure of the in vivo studies? How specific are the in vitro molecular targets? Is the chemical cytotoxic across a wide range of cells or is the response specific? Do the alternative and conventional chemicals affect the safe biological endpoints? If the endpoints are different, is one less serious? Are there differences in the ADME?

Definitions: Quantitative Structural Activity Relationships (QSAR), Absorption, Distribution, Metabolism and Excretion (ADME)

Conclusions:

This work highlights three case studies for examining the use of in vitro and in silico data for screening existing and alternative chemicals in children's consumer products based on relative hazard and exposure potential. As more United States and other governments are passing legislation to require manufactures to phase out conventional chemicals of toxicological concern, it will be increasingly important to understand the safety of alternative chemicals.

1. In vitro and QSAR databases increase coverage of toxicological data for alternative chemicals (Table 1) that may soon be replacing toxic chemicals in children's products relative to authoritative lists and reports.
2. In vitro data suggests that paraben alternatives may be safer options (Figures 2 and 3). All paraben alternatives were included in EPA's Safer Chemical Ingredients List, while no BPA or phthalate alternatives were included. Phthalates, BPA and their alternatives had similar toxicities in vitro.
3. Exposure to conventional chemicals is currently predicted to be higher than alternatives for phthalates and Bisphenol A and similar for parabens (Figure 4).

4. While the predicted functions of phthalate and BPA alternatives were broader than the conventional chemicals, parabens and their alternatives had similar predicted functions. This suggests that paraben alternatives, in addition to being less hazardous, may also be more practical substitutes.

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Supplemental Information for Chapter 3

Table S1: Data and sources for the analysis of authoritative lists, in vitro data, in silico data and in vivo data

Group	CASRN	Chemical	Alt. or Con.	ECHA Endocrine Disruption Cat.	GHS Repro tox Cat.	ToxPi Score	QSAR Dev Tox	SCIL	Fuse Highest Probable Category	Median ExpoCast Pred.#	NOAEL,HNEL or LOAEL (mg/kg/day)	CompTox Chemistry Dashboard study details and source
Bisphenols	80-05-7	BPA	C	1	1B	0.105	DT		Antioxidant (0.87)	6.30E-05	0.015	NOAEL 0.015 mg/kg/day Developmental Neurotoxicity Study Oral Rat EPA ORD ToxrefDB
Bisphenols	80-09-1	BPS	A			0.102	DT		Colorant (0.84)	8.97E-07	40	NOAEL - 40 mg/kg-day repeat dose toxicity : oral subacute rat - OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) ECHA
Bisphenols	87139-40-0/2467-02-9/620-92-8	BPF	A			0.085	DT		Antioxidant (0.74)	2.19E-08	2	NOEL* - 20 mg/kg-day repeat dose toxicity : OECD TG 407 oral subchronic rat - Chemicals Assessment Center HESS
Parabens	99-76-3	Methyl Paraben	C			0.061	NON-DT		Preservative (0.99)	2.06E-05	65	HNEL 65mg/kg/day developmental toxicity oral hamster COSMOS
Parabens	94-13-3	Propyl Paraben	C			0.106	DT		Preservative (0.96)	1.42E-05	1.20	LOAEL - 12 mg/kg-day short-term oral short-term rat - COSMOS: Short Term Toxicity RAT Wistar Oral Feed COSMOS
Parabens	120-47-8	Ethyl Paraben	C	3		0.080	DT		Preservative (0.98)	1.50E-05	NA	
Parabens	94-26-8	Butyl Paraben	C	1		0.110	DT		Preservative (0.93)	1.64E-05	1	LOAEL - 10 mg/kg-day Subchronic RAT Wistar Oral Feed COSMOS
Parabens	65-85-0	Benzoic acid	A		2	0.057	NON-DT	Green Circle	Preservative (0.94)	9.85E-05	2.5	HNEL 5mg/kg/day Developmental Oral Rat COSMOS
Parabens	24634-61-5	Potassium sorbate	A			NA	NA	Green Circle		2.47E-05	NA	
Parabens	532-32-1	Sodium benzoate	A			0.060	NA	Green Circle	Preservative (0.94)	2.98E-06	175	HNEL 175 mg/kg/day Developmental oral rat COSMOS
Parabens	110-44-1	Sorbic acid	A			0.057	DT	Green Circle	Preservative (0.93)	3.73E-05	8	HNEL 40 mg/kg/day chronic oral mouse COSMOS
Phthalates	84-44-9	phthalic anhydride	C			NA	NON-DT		Colorant (0.65)	1.32E-04	500	NOAEL 500 mg/kg/day Repeat dose oral rat ECHA IUCLID
Phthalates	117-84-0	DnOP	C	3	2	0.075	DT		Plasticizer (0.98)	1.66E-04	38.8	NOAEL - 38.8 mg/kg-day repeat dose toxicity oral rat - HPVIS
Phthalates	26761-40-0	DIDP	C	3	2	NA	NON-DT			6.92E-04	NA	

Phthalates	28553-12-0/ 68515-48-0	DINP	C	3	2	NA	DT			3.53E-04	NA	
Phthalates	84-75-3	Di-n-hexyl phthalate	C	3		0.074	NON-DT		Plasticizer (0.86)	8.50E-07	25	LOAEL 250 mg/kg-day developmental oral rat - Study ID: 5388 : Prenatal developmental toxicity study ToxRefDB
Phthalates	117-81-7	DEHP	C	1	1B	0.071	DT		Plasticizer (0.97)	2.57E-04	3.7	NOAEL - 3.7 mg/kg-day repeat dose toxicity oral rat - HPVIS
Phthalates	84-66-2	Diethyl phthalate	C	1		0.055	DT		Preservative (0.65)	9.97E-05	2.85	NOAEL 2.85 mg/kg/day Chronic oral Rat EPA ORD ToxRefDB
Phthalates	84-74-2	Dibuytl phthalate	C	1	1B	0.070	NON-DT		Plasticizer (0.74)	1.42E-04	50	NOAEL - 50 mg/kg-day developmental oral l rat - HPVIS Details HPVIS
Phthalates	85-68-7	BBP	C	1	1B	0.068	DT			1.85E-04	20	NOAEL - 20 mg/kg-day developmental oral developmental rat - HPVIS Details HPVIS
Phthalates	77-90-7	Acetyl tributyl citrate	A			0.063	DT		Flavorant (0.97)	1.18E-04	100	NOAEL - 100 mg/kg-day reproductive oral rat - HPVIS
Phthalates	166412-78-8	Di-isononyl-cyclohexane-1, 2 dicarboxylate	A			0.006	NON-DT			5.24E-08	NA	
Phthalates	6422-86-2	dioctyl terephthalate	A			0.073	DT		Plasticizer (0.97)	1.45E-05	79	NOAEL 79 mg/kg/day chronic, oral rat EPA ORD, ToxRefDB
Phthalates	8013-07-8	epoxidized soybean oil	A			NA	NA				NA	
Phthalates	91082-17-6	alkylsubphonic phenyl ester	A			0.072	NON-DT			5.41E-08	NA	
Phthalates	3319-31-1	tri-2-ethylhexyl trimellitate	A			0.093	DT		Emollient (0.88)	4.56E-05	0.67	NOAEL - 0.67 mg/kg-day repeat dose toxicity oral HPVIS Details HPVIS
Phthalates	736150-63-3	acetylated monoglycerides of fully hydrogenated caster oil	A			NA	DT				NA	
Phthalates	3198-30-9	4-benzenedicarboxylate	A			NA	DT				NA	
Phthalates	105-99-7	di-butyl adipate	A		2	0.073	NON-DT		Flavorant (0.97)		300	NOAEL - 300 mg/kg-day reproduction : oral rat - ECHA IUCLID
Phthalates	128-37-0	butylated hydroxytolulene	A		2	0.100	NON-DT		UV Absorber (0.83)	9.90E-05	25	NOAEL 25 mg/kg/day Reproduction: Oral Rat ECHA IUCLID
Phthalates		hyper branched poly, di (2 ethylhexyl) phosphate	A			NA	NA				NA	

Phthalates	78-42-2	tri (2ethylhexyl) phosphate	A			0.077	NON-DT		Plasticizer (0.87)	5.39E-05	430	NOAEL - 430 mg/kg-day repeat dose toxicity oral rat - HPVIS Details HPVIS
Phthalates	88-19-7	o-tolulene sulfonamide	A			NA	DT		Foamer (0.85)	4.14E-06	20	NOEL - 20 mg/kg-day repeat dose toxicity : OECD TG 407 oral subchronic rat - Food and Drug Safety Center HESS
Phthalates	6846-50-0	2,2,4 trimethyl 1,3 pentanediol diisobutyrate	A			0.079	DT		Catalyst (0.68)	1.98E-04	150	NOAEL - 150 mg/kg-day repeat dose toxicity : oral subchronic rat - USFDA Toxicological Principles for the Safety of Food Ingredients ECHA
Phthalates	122-62-3	diocytl sebate	A			0.075	NON-DT	Green Circle	Emollient (0.96)		NA	
Phthalates	109-43-3	dibutyl sebate	A			0.077	NON-DT		Flavorant (0.99)	1.50E-07	200	NOAEL - 200 mg/kg-day repeat dose toxicity : oral mouse - OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) ECHA
Phthalates	103-23-1	di (2- ethyl hexyl adipate)	A	3B		0.071	NON-DT		Emollient (0.88)	1.98E-04	28	NOAEL - 28 mg/kg-day developmental oral rat - HPVIS Details HPVIS

*Foot Notes: Alternative chemicals are shaded in gray. No Observable Adverse Effects Level is NOAEL, Lowest Observable Adverse Effects Level is LOAEL, Highest No Effects Level is HNEL, Lowest Effects Level is LEL. LOAELs were converted to NOAELs by dividing by a factor of 100. Toxicological Prioritization Index is ToxPi Score. *Text reads The no-observed-effect level for bisphenol F is concluded to be under 20 mg/kg per day since decreased body weight accompanied by decreased serum total cholesterol, glucose, and albumin values were observed in the female rats given 20 mg/kg per day or higher doses of bisphenol F, indicating that the reported NOAEL is actually a LOAEL and was treated as such. # for children (age 6-11) in mg/kg/day. ^indicates that the reported LOAEL is lower than the values used in ECHA risk assessments. DT is developmental toxic and NON DT is developmental non-toxic*

Table S2: Descriptions of the in vivo studies used to identify the NOAEL shown in table S1.

			In vivo Toxicity				Exposure Considerations	
Group	**Conventional or Alternative**	**Chemical**	**Endocrine**	**Repro & Devel.**	**Other**	**Non Specific**	**Repeat Dose**	**Multigen or Devel Study**
Bisphenols	Conventional	BPA		X			X	
	Alternative	BPS				X	X	
		BPF			Liver		X	
Parabens	Conventional	Methyl Paraben				X	X	
		Propyl Paraben		X			X	
		Ethyl Paraben						
		Butyl Paraben				X	X	
	Alternative	Benzoic acid		X			X	X
		Potassium sorbate		X				
		Sodium benzoate						
		Sorbic acid				X		
Phthalates	Conventional	DnOP				X	X	
		DIDP						
		DINP						
		Di-n-hexyl phthalate		X			X	X
		DEHP		X		X		
		Diethyl phthalate				X	X	X
		Dibuytl phthalate		X				
		BBP		X				
	Alternative	Aceyl tributyl citrate		X			X	
		Di-isononyl-cyclohexane-1, 2 dicarboxylate						
		dioctyl terephthalate						
		epoxidized soybean oil				X	X	

		alkylsubphonic phenyl ester						
		tri-2-ethylhexyl trimellitate						
		acetylated monoglycerides of fully hydrogenated caster oil				X	X	
		4-benzenedicarboxylate		X			X	
		di-butyl adipate		X				
		butylated hydroxytolulene		X		X	X	
		hyper branched poly, di (2 ethylhexyl) phosphate				X	X	
		tri (2ethylhexyl) phosphate				X	X	
		o-tolulene sulfonamide						
		2,2,4 trimethyl 1,3 pentanediol diisobutyrate				X	X	
		diocytl sebate		X			X	
		dibutyl sebate						
		di (2- ethyl hexyl adipate)						

Dissertation Conclusions:

This dissertation explores the prioritization of toxic chemicals in children's consumer products. Protecting children from exposure to toxic chemicals in consumer products requires identification of product chemical combinations that can most effectively reduce toxic exposure. With more than myriad of chemicals on the market, it is challenging for regulators to decide which chemicals pose the greatest threat to children's health. Further, exposure properties related to the products the chemicals are found in is important for focusing regulatory action to maximize exposure reduction.

In the first chapter, we prioritized chemicals based on toxicity and the potential for exposure in children's products. This work was based on the data reported by manufacturers as required by Washington State's Children's Safe Product Act (CSPA). Overall, this framework provides one method of prioritizing chemicals and products that may be of concern for children's health. Based on the results of this framework, formaldehyde, DBP and styrene should be considered for future action to help reduce the potential for children's exposure through commercial products. When parabens and phthalates are considered as groups, phthalates join along with formaldehyde and styrene as the highest priority chemical groups. Other prioritization tools, such as ToxPi, suggest prioritization of parabens and octamethylcyclotetrasiloxane.

The second chapter assessed the agreement of the CSPA database used in the first chapter, to the Product Testing Database developed by Washington State Department of Ecology. While many states have implemented required reporting frameworks for chemicals in children's products, Washington also has a product testing database which independently tests children's products for toxic chemicals and makes the data publicly available. In general, we observe that the CSPA-MD has higher concentrations of chemicals of high concern to children than the PTD. When we focus on chemicals with concentration limits in children's products, we find that the percentage of product-family component chemical combinations that are higher in the PTD than the CSPA-MD increases from 19% to 35%. This suggests that restricted chemicals may be less likely to be over-reported.

The final chapter highlights three case studies for examining the use of in vitro and in silico data for screening existing and alternative chemicals in children's consumer products based on relative hazard and exposure potential. As more United States and other governments are passing legislation to require manufactures to phase out conventional chemicals of toxicological concern, it will be increasingly important to understand the safety of alternative chemicals. We found that QSAR and in vitro databases increase coverage of toxicological data for alternative chemicals that may soon be replacing toxic chemicals in children's products relative to authoritative lists and reports. In vitro data suggests that paraben alternatives may be safer options. All paraben alternatives were included in EPA's Safer Chemical Ingredients List, while only 2 out of 17 of the phthalate alternatives and no bisphenol A alternatives were included. Phthalates and their alternatives had similar toxicities in vitro, but high NOAELs, suggesting they may be less toxic. BPA and its alternatives had similar toxicities both in vitro and in vivo.

Taken together, the results of this dissertation demonstrate how prioritization tools can be used to translate the results of complex databases (e.g. CSPA-MD, PTD, ToxCast) for public health decision making. For example, phthalates in children's products were investigated in every chapter of this dissertation. Under the first aim, phthalates were identified as a high priority based on their toxicity and use in children's products with high potential for exposure. In the second aim, we found that phthalates were among the restricted chemicals less likely to be reported in higher concentrations by manufacturers than measured by the Department of Ecology. In the third aim, the toxicity of phthalates and their alternatives were investigated. We found that in general, toxicity information on phthalates was more likely to be available using in vitro data compared to animal studies. In vitro data suggested little difference in toxicity between phthalates and their alternatives. These results suggest that phthalates and their

alternatives in children's products are an important area for continued action and research. The results of this dissertation can be used to prioritize product-chemical combinations to reduce children's exposure to toxic chemicals.