International Journal of
Environmental Research and Public Health

MDPI

Article

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

Marissa N. Smith [1], Joshua Grice [2], Alison Cullen [3] and Elaine M. Faustman [1,*]

[1] Department of Environmental and Occupational Health Sciences, Institute for Risk Analysis and Risk Communications, University of Washington, Seattle, WA 98105, USA; rissa8@u.washington.edu
[2] Washington State Department of Ecology, Olympia, WA 98504, USA; joshua.grice@gmail.com
[3] Evans School of Public Policy and Governance, University of Washington, Seattle, WA 98195, USA; alison@u.washington.edu
* Correspondence: faustman@u.washington.edu; Tel.: +1-206-685-2269

Academic Editors: Helena Solo-Gabriele and Alesia Ferguson
Received: 1 February 2016; Accepted: 12 April 2016; Published: 19 April 2016

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.

Keywords: chemical prioritization; ToxCast; ExpoCast; consumer products; children's health

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 (CSPA) 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 (DBP) 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 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. 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 and developmental toxicity, and endocrine disruption as toxicity endpoints [14]. 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 childcare. 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 to 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 metal 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 chemicals are scored on a scale of zero to three for the following attributes: 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.

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). Variables for the exposure score are in bold and variables for the toxicity score are not in bold.

Variable	Equation Abbrev.	Score			Basis	Mathematical Role
		1	2	3		
Lifestage	**LS**	**Ages 3–12**	**NA**	**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)** [16]	**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)** [17]	**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**	**<3.39 × 10^{-3}**	**3.4 × 10^{-3}–6.67 × 10^{-3}**	**>6.7 × 10^{-3}**	**Based on the tertiles of the Kp** [18,19]	**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)** [17]	**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 °C	**VP**	**<0.075 mmHg**	**0.075–32 mmHg**	**> 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)** [17]	**Averages with VP for inhalation exposure toxicokinetics**
Reproductive and developmental toxicity certainty #	$RD_{certainty}$	Potential RD ^	Suspected RD ^	Known RD	ECHA Existing Substances [20], Prop 65 [21], Global Harmonization Standard [22]	Multiplies with $RD_{potency}$
Reproductive and developmental potency	$RD_{potency}$	NOAEL > 397 mg/kg	NOAEL 200–297 mg/kg	NOAEL < 200 mg/kg	NOAEL from ECHA Existing Substances [20]	Modifying factor $RD_{certainty}$

Table 1. *Cont.*

Variable	Equation Abbrev.	Score			Basis	Mathematical Role
		1	2	3		
Carcinogenicity certainty #	$C_{certianty}$	Potential Carcinogen ^	Suspected Carcinogen ^	Known Carcinogen ^	IARC [23], Prop 65 [21], Global Harmonization Standard [22], EPA IRIS [24]	Multiplies with $C_{potency}$
Carcinogenicity potency	$C_{potency}$	TD50 > 465 mg/kg	TD50 from 233 to 465 mg/kg	TD50 < 233 mg/kg	Dose that causes a tumor in 50% of the study population (TD50) from the Carcinogenic Potency Database [25,26]	Modifying factor for $C_{certainty}$
Endocrine disruption certainty #	$ED_{certianty}$	Potential ED ^	Suspected ED ^	Known ED	ECHA Endocrine Disruptor Substances of Concern [27], Global Harmonization Standard [22]	Multiplies with $ED_{potency}$
Endocrine disruptor potency	$ED_{potency}$	NOAEL > 336 mg/kg	NOAEL 336–667 mg/kg	NOAEL < 667 mg/kg	LOAEL from ECHA Endocrine Disruptor Substances of Concern [27]	Modifying factor for $ED_{certainty}$
Neurotoxicity certainty #	$NT_{certainty}$			Known NT	Grandjean and Landrigan *et al.* (2014) [28], Global Harmonization Standard [22]	Multiplies with $NT_{potency}$
Neurotoxicity potency	$NT_{potency}$	All NTs			All known neurotoxicants are assigned a score of 2	Modifying factor for $NT_{certainty}$

* For chemical concentrations under 100 ppm a score of 0.5 was assigned, for chemical concentrations between 500 and 1000 ppm a score of 1.5 was assigned and for chemical concentrations between 5000 and 10,000 ppm 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.

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.

Chemical	Observed Oral Absorption Score	Observed Dermal Absorption Score	Observed 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	1	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.

2.3. Framework Equations

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 increases 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. Each of the components and equations are explained in detail below.

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.

$$\begin{aligned}\text{Exposure Score} = (\text{LS} + \text{EX} + \text{A} + \text{Con}) + [(\text{O}_{\text{MF}}(\text{S} + \text{Abs}_{\text{oral}})/2) + \\ (\text{I}_{\text{MF}}(\text{VP} + \text{Abs}_{\text{inhalation}})/2) + (\text{D}_{\text{MF}}(\text{K}_{\text{p}} + \text{Abs}_{\text{dermal}})/2]\end{aligned} \quad (1)$$

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.

$$\begin{aligned}\text{Toxicity Score} = (\text{ED}_{\text{certainty}} \times \text{ED}_{\text{potency}}) + (\text{RD}_{\text{certainty}} \times \text{RD}_{\text{potency}}) + (\text{C}_{\text{certainty}} \times \text{C}_{\text{potency}}) \\ + (\text{NT}_{\text{certainty}} \times \text{NT}_{\text{potency}})\end{aligned} \quad (2)$$

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.

$$\text{Total Priority Index} = \text{Exposure Score} \times \text{Toxicity Score} \quad (3)$$

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.

$$\text{Endocrine Disruptor Score} = \text{Exposure Score} \times \text{ED}_{\text{certainty}} \times \text{ED}_{\text{potency}} \quad (4)$$

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.

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 (Tables 1 and 2).

2.4.2. 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 0.075 and 32 mmHg 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 (>0.01 mol/L) were assigned a score of 3 [16].

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 [18,19]. 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. Observed 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 [15]. 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 [27]. This list was created to prioritize chemicals for further review. Substances are categorized from 1 to 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 [22], the European Union's Existing Substances Regulation [20], and the Proposition 65 List [21]. 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 [21]. 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 European Union 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 [23], The EPA's Integrated Risk Information System (IRIS) database [24], 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 [28] 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 22 January 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 22 January 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 [29]. 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 [26]. 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.

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 [30,31]. The system is based on fate and transport models of contaminants in environmental sources, such as air, water and soil that can then be used to predict human exposures and correlates with the National Health and Nutrition Examination Survey (NHANES) biomonitoring levels, especially for chemicals found in consumer products [30]. 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 8000 compounds [31]. Median predicted exposures in mg/kg/day were available for all CSPA chemicals except formaldehyde. For metals reported in CSPA as groups, all metal 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 [32]. Filer *et al*. (2014) report ToxPi scores for 1858 chemicals available in phase II of ToxCast [33]. In addition to the original sources of endocrine disruption considered in Reif *et al*. (2013), Filer *et al*. (2014) [32,33] also considered assays for glucocorticoid disruption and peroxisome proliferator-activated receptor (PPAR) activation 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) [33] 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 DBP (24), diethylhexyl phthalate 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.

DBP, 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.

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 in bold. 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 and 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 and Antimony compounds	3378	10.3 ± 1.4	31.0 ± 4.3
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 and 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

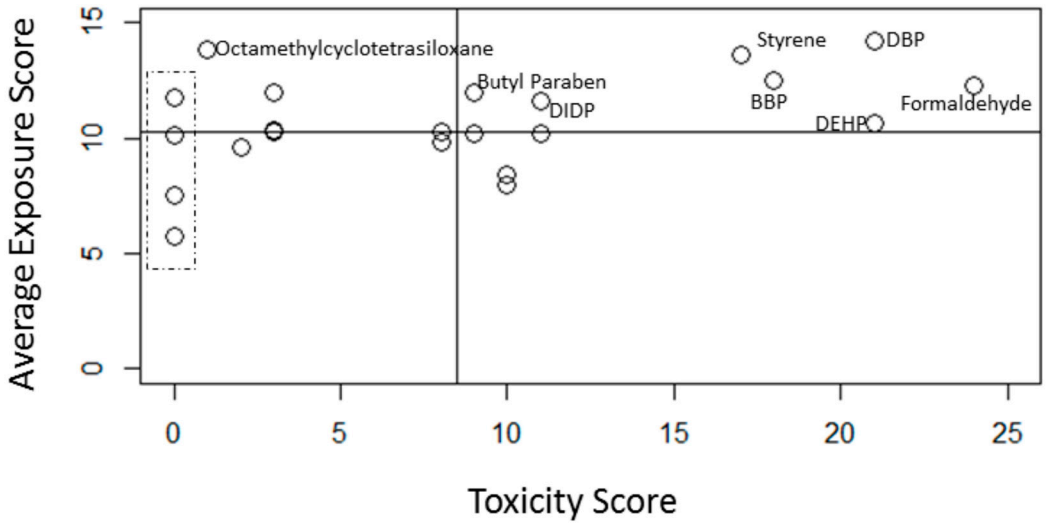

Figure 1. Scatterplot showing the relationship between toxicity and average exposure scores for chemicals in the CSPA framework. The scatterplot is divided into quadrants with lines drawn at the median exposure score (horizontal line) and median toxicity score (vertical line) to emphasize that chemicals 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, benzyl butyl phthalate (BBP), DBP and DEHP all fall in the highest priority quadrant in this figure. Other phthalates, diisodecyl phthalate (DIDP) and di-n-hexyl phthalate (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), DBP (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, BBP, DnHP, DBP 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.

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.

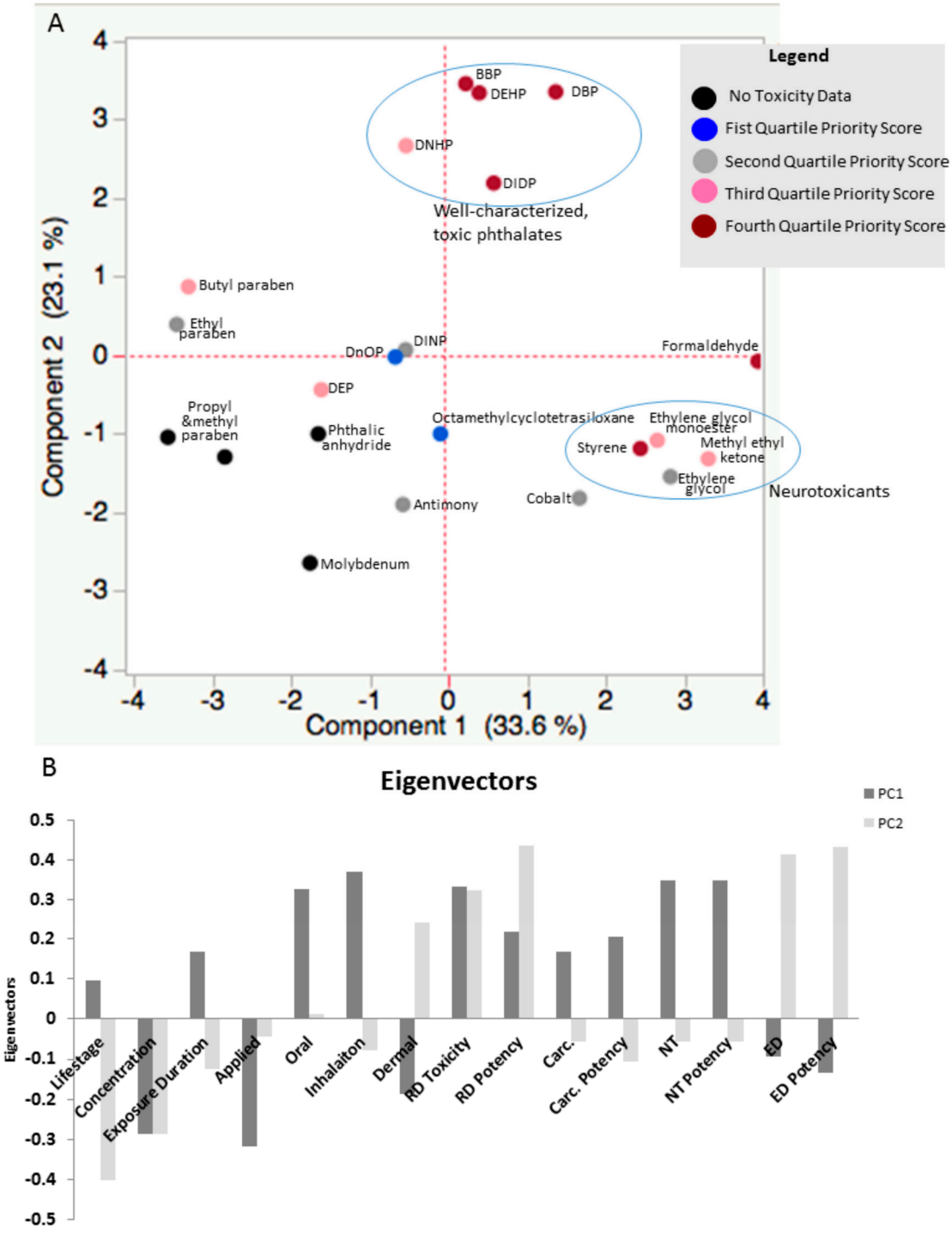

Figure 2. Principal Components Analysis score plot (**A**) and eigenvector plot (**B**) for variables in the CSPA framework. The first two principal components explain ~56% of the variability in total priority index between chemicals. A positive value in the score plot shown in Figure 2A for PC1 is associated 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.

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	14,551
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) [33] applied ToxPi for the prioritization 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 ToxPi scores calculated by Filer *et al*. (2014) [33]. 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 (Figure 3A). Octamethylcyclotetrasiloxane 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 [30]. 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 3B). Other chemicals, like styrene, have higher exposure scores relative to those predicted using ExpoCast. Two phthalates, diisononyl phthalate (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.

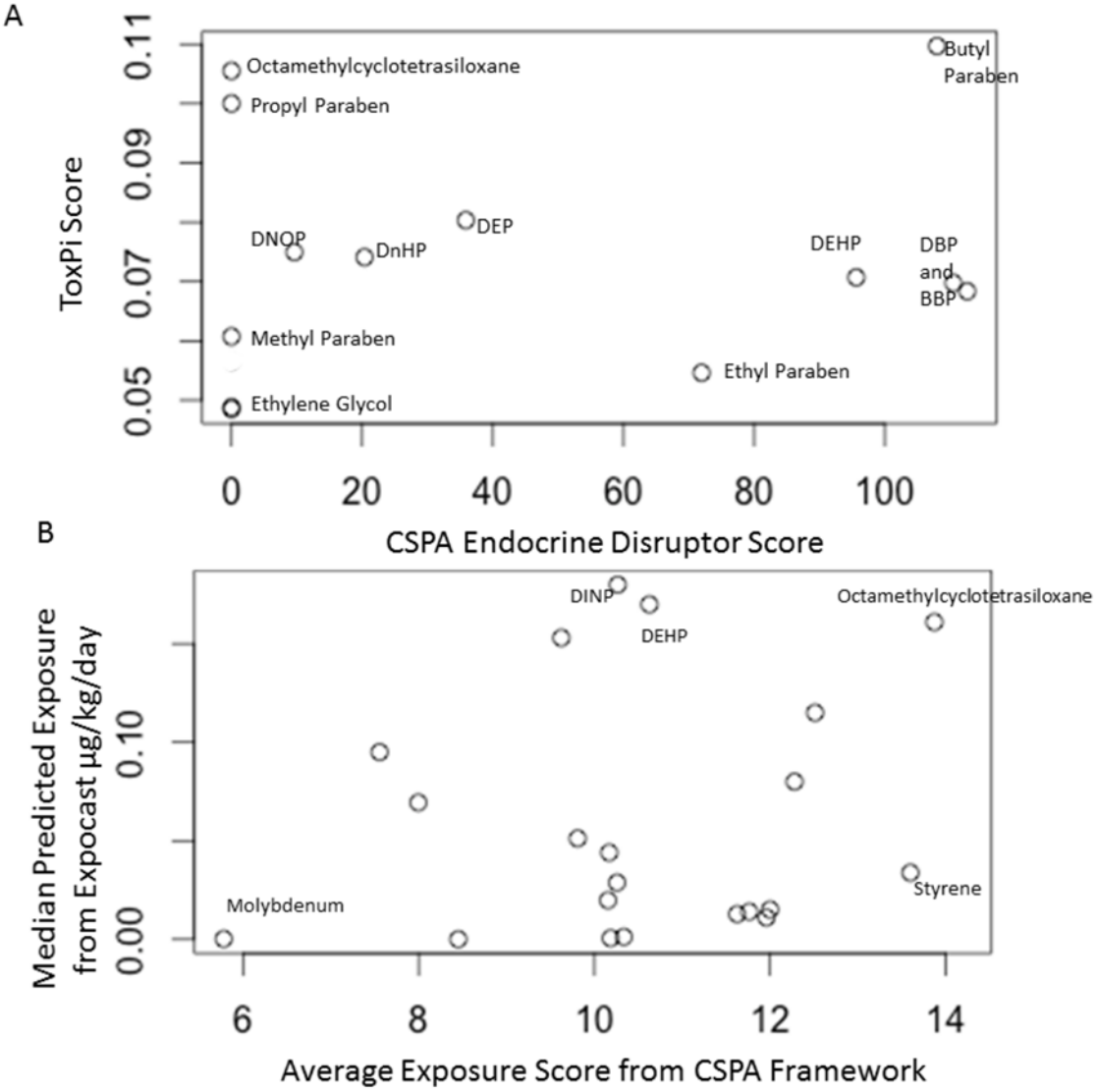

Figure 3. Comparison of CSPA endocrine disruptor score to ToxPi scores (**A**) and comparison of CSPA exposure score to ExpoCast score (**B**). Butyl paraben scores relatively high using both the CSPA endocrine disruptor score and the ToxPi score. DEHP and DBP score higher using the CSPA framework than 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, Table 2 and Table 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, DBP, BBP, DEHP, 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 DBP 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 Existing Substance Endocrine Disruptor Database (ECHA) that was used to calculate 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 [30]. 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 either (1) toxic to biological systems not considered in this framework; (2) toxicologically characterized by databases not included in either this framework such asREPROTEXT [34]; or (3) 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 metal compounds. Because metal 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. As chemical reporting requirements become more common and more consumer product databases are developed, prioritization of the data based on both exposure potential and toxicity, as can be done using this framework, will be critical. This increase in reporting frequency requirements will also be met with a need for more stakeholder engagement through focus groups and value based decision analytics to ensure that the models are answering the right regulatory questions [35–37].

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. Instead, it indicates a difference in rank. 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 these 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 be employed, along with other prioritization tools, such as ToxPi and ExpoCast.

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. Because this framework relies on existing data sources, it will continue to grow as more information is added to these sources. Additional data on chemical potency that is both uniform and consistent will strengthen this framework. High-throughput *in vitro* tests provide consistency across a high volume of chemicals. As these techniques become more widely available and adverse outcome pathways are available for interpretation of molecular changes, it may be possible to assess chemical potency in a uniform and consistent manner across all chemicals. This framework provides a flexible resource chemical prioritization that is capable of growing with the scientific literature and available databases.

Supplementary Materials: The following are available online at www.mdpi.com/www.mdpi.com/1660-4601/13/4/431/s1, Table S1. Total number of reports in the CSPA database from August 2012 to September 2015 by chemical. Chemicals shown in bold are included in the analyses for this paper. These chemicals represent approximately 88% of the database as a whole. Table S2. Potency factor scores and sources for reproductive and developmental toxicants and endocrine disruptors. 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.

Acknowledgments: This publication/poster was made possible by the Washington State Department of Ecology, USEPA grants 83573801 and 83451401, and NIEHS Award #5P01ES009601. Its contents are solely the responsibility of the grantee and do not necessarily represent the official views of the USEPA. Further, USEPA does not endorse the purchase of any commercial products or services mentioned in the publication.

Author Contributions: All of the authors made significant contributions to this work. Marissa N. Smith and Elaine M. Faustman conceived of the framework and executed its construction. Marissa N. Smith wrote the manuscript and created the figures under the direction of Alison Cullen and Elaine M. Faustman. Joshua Grice identified the key questions, facilitated accession of CSPA data and previous work and contributed to data analysis and framework construction. Alison Cullen contributed to framework construction and the statistical data analysis.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

Agency for Toxic Substances and Disease Research	ATSDR
Butyl benzyl phthalate	BBP
Carcinogenicity	Carc
Children's Safe Product Act	CSPA
Di-2-ehtylhexyl phthalate	DEHP
Dibutyl phthalate	DBP
Diethyl phthalate	DEP
Diisodecyl phthalate	DIDP
Diisononyl phthalate	DINP
Di-n-Hexyl phthalate	DNHP
Di-n-octyl phthalate	DnOP
Endocrine Disruption	ED
European Chemical Agency	ECHA
Globally Harmonized System	GHS
Integrated Risk Information System	IRIS
International Agency for Research on Cancer	IARC
Lowest Observable Adverse Effects Level	LOAEL
Neurotoxicity	NT
No Observable Adverse Effects Level	NOAEL
Reference Dose	RfD
Reproductive and Developmental Toxicity	RD

Toxicological Prioritization Index	ToxPi
Tumor Dose$_{50}$	TD_{50}
United States Environmental Protection Agency	EPA
Washington State Department of Ecology	Ecology

References

1. Houlihan, J.; Kropp, T.; Wiles, R.; Gray, S.; Campbell, C. Body Burden—The Pollution in Newborns a Benchmark Investigation of Industrial Chemicals, Pollutants, and Pesticides in Umbilical Cord Blood. Available online: https://repository.library.georgetown.edu/handle/10822/980233 (accessed on 1 February 2016).
2. Becker, M.; Edwards, S.; Massey, R.I. Toxic chemicals in toys and children's products: Limitations of current responses and recommendations for government and industry. *Environ. Sci. Tech.* **2010**, *44*, 7986–7991. [CrossRef] [PubMed]
3. Schettler, T. Human exposure to phthalates via consumer products. *Int. J. Androl.* **2006**, *29*, 134–139. [CrossRef] [PubMed]
4. Babich, M.A.; Chen, S.B.; Greene, M.S.; Kiss, C.T.; Porter, W.K.; Smith, T.P.; Zamula, W.W. Risk assessment of oral exposure to diisononyl phthalate from children's products. *Reg. Toxicol. Pharm.* **2004**, *40*, 151–167. [CrossRef] [PubMed]
5. Maas, R.P.; Patch, S.C.; Pandolfo, T.J.; Duhan, J.L.; Gandy, N.F. Lead content and exposure from children's and adult's jewelry products. *Bull. Environ. Contamin Toxicol.* **2005**, *74*, 437–444. [CrossRef]
6. Sathyanarayana, S.; Karr, C.J.; Lozano, E.B.; Brown, E.; Calafat, A.M.; Swan, S.H. Baby care products: Possible sources of infant phthalate exposure. *Pediatrics* **2008**, *121*, e260–e268. [CrossRef] [PubMed]
7. Chen, S.J.; Ma, Y.J.; Wang, J.; Chen, D.; Luo, X.J.; Mai, B.X. Brominated flame retardants in children's toys: Concentration, composition, and children's exposure and risk assessment. *Environ. Sci. Technol.* **2009**, *43*, 4200–4206. [CrossRef] [PubMed]
8. Faustman, E.M.; Silbernagal, S.M.; Fenske, R.A.; Burbacher, T.M.; Ponce, R.A. Mechanisms underlying children's susceptibility to environmental toxicants. *Environ. Health Perspect.* **2000**, *108* (Suppl 1), 13–21. [CrossRef] [PubMed]
9. Allen, J.G.; McClean, M.D.; Stapleton, H.M.; Webster, T.F. Linking PBDEs in house dust to consumer products using X-ray fluorescence. *Environ. Sci. Technol.* **2008**, *42*, 4222–4228. [CrossRef] [PubMed]
10. Wu, N.; Herrmann, T.; Paepke, O.; Tickner, J.; Hale, R.; Harvey, E.; La Guardia, M.; McCLean, M.R.; Webster, T.F. Human exposure to PBDEs: Associations of PBDE body burdens with food consumption and house dust concentrations. *Environ. Sci. Tech.* **2007**, *41*, 1584–1589. [CrossRef]
11. Bellinger, D.C. Very low lead exposures and children's neurodevelopment. *Curr. Opin. Pediatr.* **2008**, *20*, 172–177. [CrossRef] [PubMed]
12. Counter, S.A.; Buchanan, L.H. Mercury exposure in children: A review. *Toxicol. Appl. Pharm.* **2004**, *198*, 209–230. [CrossRef] [PubMed]
13. Landrigan, P.J.; Schechter, C.B.; Lipton, J.M.; Fahs, M.C.; Schartz, J. Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environ. Health Perspect.* **2002**, *110*, 721–728. [CrossRef] [PubMed]
14. Stone, A.; Delistraty, D. Sources of toxicity and exposure information for identifying chemicals of high concern to children. *Environ. Impt. Assess. Rev.* **2010**, *30*, 380–387. [CrossRef]
15. Children's Safe Product Act, 2016. Available online: http://www.ecy.wa.gov/programs/hwtr/RTT/cspa/ (accessed on 30 January 2016).
16. Savjani, K.T.; Gajjar, A.K.; Savjani, J.K. Drug solubility: Importance and enhancement Techniques. *ISRN Pharm.* **2012**. [CrossRef] [PubMed]
17. Toxic Substances Portal Toxicological Profiles, 2015. Available online: http://www.atsdr.cdc.gov/toxprofiles/index.asp (accessed on 30 January 2016).
18. Center for Disease Control and Prevention. Skin Permeation Calculator 2009. Available online: http://www.cdc.gov/niosh/topics/skin/skinpermcalc.html (accessed on 30 January 2016).

19. Potts, R.O.; Guy, R.H. Predicting skin permeability. *Pharm. Res.* **1992**, *9*, 663–669. [CrossRef] [PubMed]
20. European Chemical Agency. Endocrine Disruptions: Substances of Concern, 2015. Available online: http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm#priority_list (accessed on 30 January 2016).
21. California Environmental Protection Agency, United States. Chemicals Known to the State to Cause Cancer or Reproductive Toxicity. Available online: http://oehha.ca.gov/prop65/prop65_list/files/P65single012315.pdf (accessed on 28 January 2016).
22. National Institute of Technology Evaluation, Japan. Global Harmonization System, 2013. Available online: http://www.safe.nite.go.jp/english/ghs/h25_mhlw_list_e.html (accessed on 21 January 2016).
23. International Agency for Research on Cancer, Word Health Organization. Agents Classified by the IARC Monographs, 2015. Available online: http://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf (accessed on 29 January 2016).
24. Environmental Protection Agency, United States. Integrated Risk Information Systems, 2016. Available online: http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showSubstanceList&list_type=alpha&view=D (accessed on 29 January 2016).
25. Fiori, J.M.; Meyerhoff, R.D. Extending the threshold of regulation concept: De minimis limits for carcinogens and mutagens. *Reg. Toxicoland Pharm.* **2002**, *35*, 209–216. [CrossRef] [PubMed]
26. ToxNet, National Library of Medicine, United States. Carcinogenic Potency Database, 2011. Available online: http://toxnet.nlm.nih.gov/newtoxnet/cpdb.htm (accessed on 10 January 2016).
27. Eurpoean Chemical Agency. Information from the Existing Substances Regulation, 2007. Available online: http://echa.europa.eu/information-on-chemicals/information-from-existing-substances-regulation?p_p_id=viewsubstances_WAR_echarevsubstanceportlet&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_pos=1&p_p_col_count=2&_viewsubstances_WAR_echarevsubstanceportlet_keywords=&_viewsubstances_WAR_echarevsubstanceportlet_advancedSearch=false&_viewsubstances_WAR_echarevsubstanceportlet_andOperator=true&_viewsubstances_WAR_echarevsubstanceportlet_orderByCol=synonymDynamicField_546&_viewsubstances_WAR_echarevsubstanceportlet_orderByType=asc&_viewsubstances_WAR_echarevsubstanceportlet_delta=200 (accessed on 15 January 2016).
28. Grandjean, P.; Landrigan, P.J. Neurobehavioural effects of developmental toxicity. *Lancet Neurol.* **2014**, *13*, 330–338. [CrossRef]
29. National Toxicology Program, United States. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Di-n-Octyl Phthalate (DnOP). 2003. Available online: https://ntp.niehs.nih.gov/ntp/ohat/phthalates/dnop/dnop_monograph_final.pdf (accessed on 30 January 2016).
30. Wambaugh, J.F.; Setzer, W.R.; Reif, D.M.; Sumit, G.; Mitchell-Blackwood, J.; Arnot, J.A.; Joliet, O.; Frame, A.; Rabinowitz, J.; Knudson, T.; *et al.* High-throughput models for exposure-based chemical prioritization in the ExpoCast project. *Environ. Sci. Technol.* **2013**, *47*, 8479–8488. [CrossRef] [PubMed]
31. Wambaugh, J.F.; Wang, A.; Dionisio, K.L.; Frame, A.; Egeghy, P.; Judson, R.; Woodrow Setzer, R. High throughput heuristics for prioritizing human exposure to environmental chemicals. *Environ. Sci. Technol.* **2014**, *48*, 12760–12767. [CrossRef] [PubMed]
32. Reif, D.M.; Sypa, M.; Lock, E.F.; Wright, F.A.; Wilson, A.; Cathey, T.; Judson, R.R.; Rusyn, I. ToxPi GUI: An interactive visualization tool for transparent integration of data from diverse sources of evidence. *Bioinformatics* **2013**, *29*, 402–403. [CrossRef] [PubMed]
33. Filer, D.; Patisaul, H.; Schug, T.; Reif, D.; Thayer, K. Test driving ToxCast: endocrine profiling for 1858 chemicals included in phase II. *Curr. Opin. Pharm.* **2014**, *19*, 145–152. [CrossRef] [PubMed]
34. REPROTEXT® Database. Available online: http://www.micromedexsolutions.com/micromedex2/4.34.0/WebHelp/Document_help/Reprotext_document.htm (accessed on 1 February 2016).
35. Drew, C.H.; Grace, D.A.; Silbernagel, S.M.; Hemmings, E.S.; Smith, A.; Griffith, W.C.; Takaro, T.K.; Faustman, E.M. Nuclear waste transportation: Case studies of identifying stakeholder risk information needs. *Environ. Health Perspect.* **2003**, *111*, 263–272. [CrossRef] [PubMed]

36. Mitchell, J.; Pabon, N.; Collier, Z.A.; Egeghy, P.P.; Cohen-Hubal, E.; Linkov, I.; Vallero, D.A. A decision analytic approach to exposure-based chemical prioritization. *PLoS ONE* **2013**, *8*, e70911. [CrossRef] [PubMed]
37. Hamilton, J.D.; Dagget, D.A.; Pittinger, C.A. The role of professional judgment in chemical hazard assessment and communication. *Regul. Toxicol. Pharmacol.* **2006**, *46*, 84–92. [CrossRef] [PubMed]

© 2016 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).