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

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

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Children's Safe Product Act (CSPA)

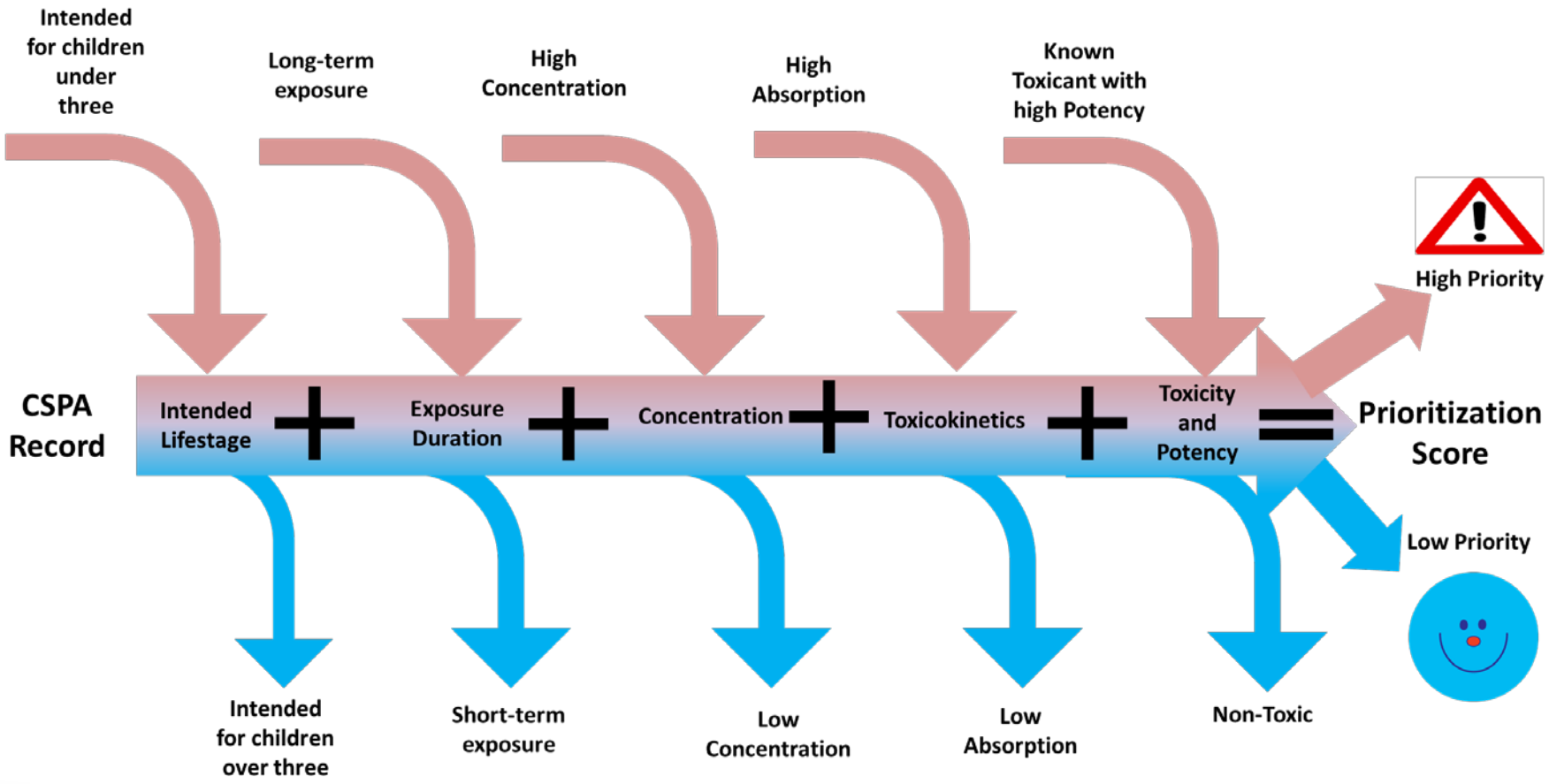
- CSPA was passed in 2008 in Washington State
- CSPA requires that manufacturers report the presence of 66 Chemicals of High Concern to Children in children's products sold in WA state
  - Target age group (under age three, age three and above)
  - Chemical Function
  - Product Category
  - Concentration Range

Chemical concentration range
Range 1: < 100 ppm and >= PQL
Range 2: < 500 ppm and >= 100 ppm
Range 3: < 1000 ppm and >= 500 ppm
Range 4: < 5000 ppm and >= 1000 ppm
Range 5: < 10,000 ppm and >= 5000 ppm
Range 6: >= 10000 ppm

Chemicals of High Concern to Children (CHCC)

Example Chemicals of High Concern to Children			
Formaldehyde	Molybdenum & molybdenum compounds	Di-2-ethylhexyl phthalate	Phthalic Anhydride
Methyl ethyl ketone	Antimony & Antimony compounds	Di-n-octyl phthalate (DnOP)	Butyl Benzyl phthalate (BBP)
Methyl paraben	Octamethylcyclotetrasiloxane	Diethyl phthalate	Diisodecyl phthalate (DIDP)
Propyl paraben	Cobalt & cobalt compounds	Dibutyl phthalate	Diisononyl phthalate (DINP)
Ethyl paraben	Styrene	Ethylene glycol	Di-n-Hexyl Phthalate
Butyl paraben		Ethylene glycol monoethyl ester	

What Matters in Prioritizing CSPA Chemicals?



How to we integrate this information?

- At the time of this work, CSPA had generated over 33K records
- We developed a framework that mathematically combine variables about the product and chemical in each CSPA report
- Three scores can be calculated:
  - Exposure score
  - Toxicity score
  - Total priority index

Exposure Score Variables

- Each variable was assigned a score between 1 and 3 with three indicating a higher priority
- Variables included:

Lifestage
Concentration
Applied Directly to Skin
Exposure Duration
Exposure Routes
Absorption

CSPA

LogP
Solubility
Vapor Pressure

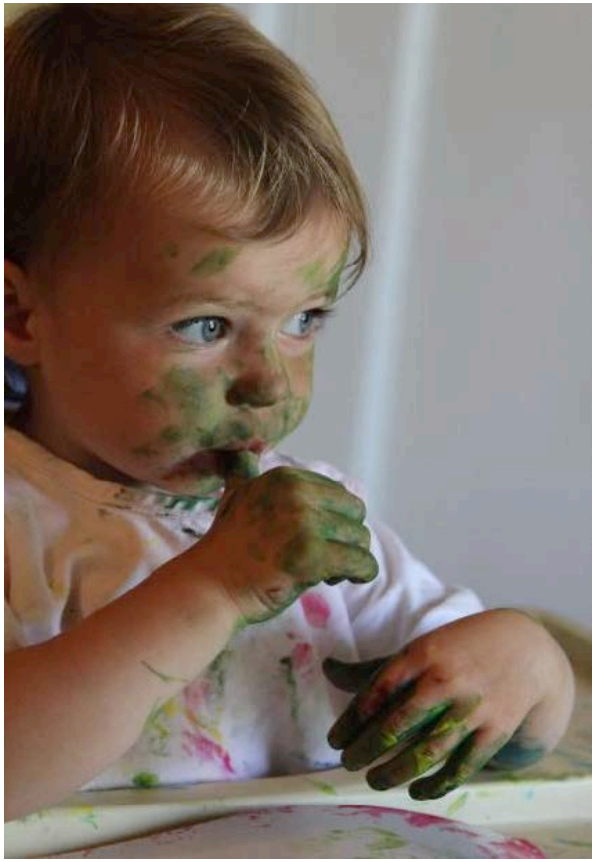
Variable Scoring From CSPA-Product Features

Lifestage: Age three and above=1, under age three=3

Concentration: From 0.5-3 based on the 6 ranges presented earlier

Exposure Duration: Short-term=1, long-term=2

Applied directly to skin or body: Yes=3, no=1



Exposure Score Variables

- Each variable was assigned a score between 1 and 3 with three indicating a higher priority
- Variables included:

Lifestage
Concentration
Accessibility
Exposure Duration
Exposure Routes
Absorption

LogP
Solubility
Vapor Pressure

Variable Scoring: Exposure Routes

Based on the Product Segment or Brick level

Exposure Routes: Oral, Dermal and Inhalation routes were assigned primary, secondary and tertiary routes.

- For example: a plastic cup would have a primary oral exposure route, secondary dermal and tertiary inhalation
- The tertiary inhalation includes potential exposure from house dust, as consumer products disintegrate
- For children under 3, a secondary oral exposure route was assigned for all products

Variable Scoring

- Each variable was assigned a score between 1 and 3 with three indicating a higher priority
- Variables included:

Lifestage
Concentration
Accessibility
Exposure Duration
Exposure Routes
Absorption

Dermal Permeability
Solubility
Vapor Pressure

Exposure Score Factors From Table 1

Variable	Equation Abbrev.	Score			Basis
		1	2	3	
Oral exposure	O_{MF}	Tertiary	Secondary	Primary	Product segment (primary), Target age (secondary) [15]
Water solubility (moles/L)	S	<0.001	0.001–0.01	>0.1	Soluble (3), moderately soluble (2), insoluble (1) [16]
Oral absorption	Abs_{oral}	1%–5%	Absorbed at unknown rate	Above 5%	Absorption rate through oral exposure (ATSDR) [17]
Dermal exposure	D_{MF}	Tertiary	Secondary	Primary	As reported product segment (primary) [15]
Dermal permeability constant	K_p	$<3.39 \times 10^{-3}$	3.4×10^{-3}–6.67×10^{-3}	$>6.7 \times 10^{-3}$	Based on the tertiles of the Kp [18,19]
Dermal exposure absorption	Abs_{dermal}	1%–5%	Absorbed at unknown rate	Above 5%	Absorption rate through dermal exposure (ATSDR) [17]
Inhalation exposure	I_{MF}	Tertiary	Secondary	Primary	As reported product segment [15]
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)
Inhalation exposure absorption	$Abs_{inhalation}$	1%–5%	Absorbed at unknown rate	Above 5%	Absorption rate through inhalation exposure (ATSDR) [17]

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Exposure Score

From CSPA

(Lifestage+Exposure Duration+Applied to Skin+ Concentration)+

Is Oral a Primary, Secondary or Tertiary Exposure Route?

[(Oral Exposure Modifying Factor (Water Solubility+ Oral Absorption)/2) +

Is Inhalation a Primary, Secondary or Tertiary Exposure Route?

(Inhalation Exposure Modifying Factor (Vapor Pressure + Inhalation Absorption)/2) +

Is Dermal a Primary, Secondary or Tertiary Exposure Route?

(Dermal Exposure Modifying Factor (Dermal Permeability + Dermal Absorption)/2]

= Exposure Score

Toxicity Score Factors From Table 1

Variable	Equation Abbrev.	Score			Basis
		1	2	3	
Reproductive and developmental toxicity certainty #	$RD_{certainty}$	Potential RD ^	Suspected RD ^	Known RD	ECHA Existing Substances [20], Prop 65 [21], Global Harmonization Standard [22]
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]
Carcinogenicity certainty#	$C_{certianty}$	Potential Carcinogen ^	Suspected Carcinogen^	Known Carcinogen ^	IARC [23], Prop 65 [21], Global Harmonization Standard [22], EPA IRIS [24]
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]
Endocrine disruption certainty #	$ED_{certianty}$	Potential ED ^	Suspected ED ^	Known ED	ECHA Endocrine Disruptor Substances of Concern [27], Global Harmonization Standard [22]
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 [27]
Neurotoxicity certainty #	$NT_{certainty}$			Known NT	Grandjean and Landrigan *et al.* (2014) [28] , Global Harmonization Standard [22]
Neurotoxicity potency	$NT_{potency}$		All NTs		All known neurotoxicants are assigned a score of 2

Integration of Scores

Sum to create the toxicity score

Endocrine Disruption Score=
*Certainty*Potency*

Reproductive and Developmental Toxicity Score=
*Certainty*Potency*

Carcinogenesis Score =
*Certainty*Potency*

Neurotoxicity Score =
*Certainty*Potency*

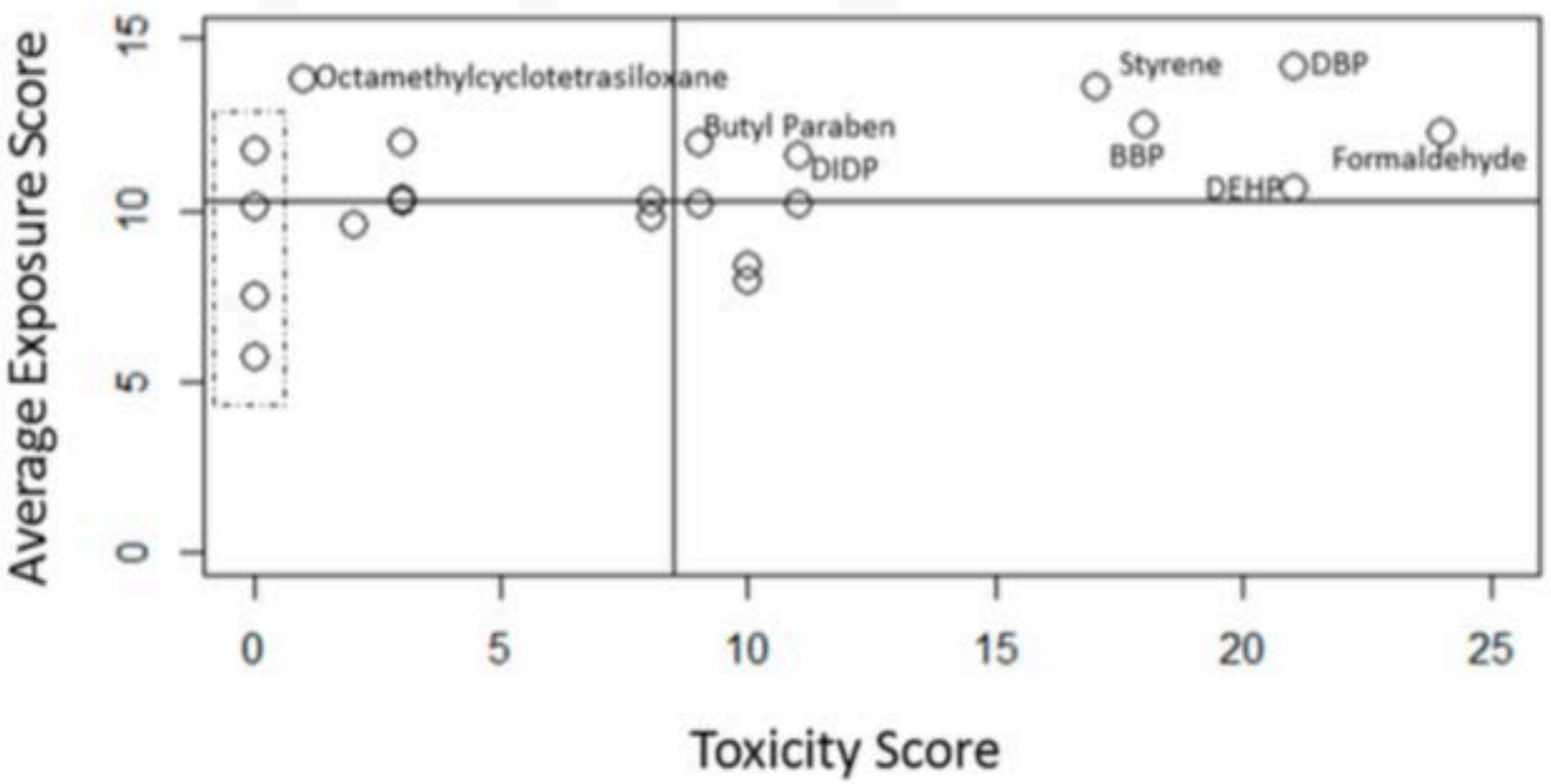
Total Priority Index= *Exposure Score*Toxicity Score*

Interpretation of Results

- The scoring results are designed to interpret the CSPA data relative to itself.
- Higher scoring products are a greater concern
- However, when no health outcome data is present records the total priority score is 0 points.
  - Molybdenum, some phthalates, and some parabens
- These chemicals require more information before they can be fully prioritized, as of now, however the exposure score can be used to look at the potential for high exposures in children.

High Priority Chemicals

- Formaldehyde, Styrene and dibutyl phthalate have the highest total priority scores and are also found in the upper right hand corner



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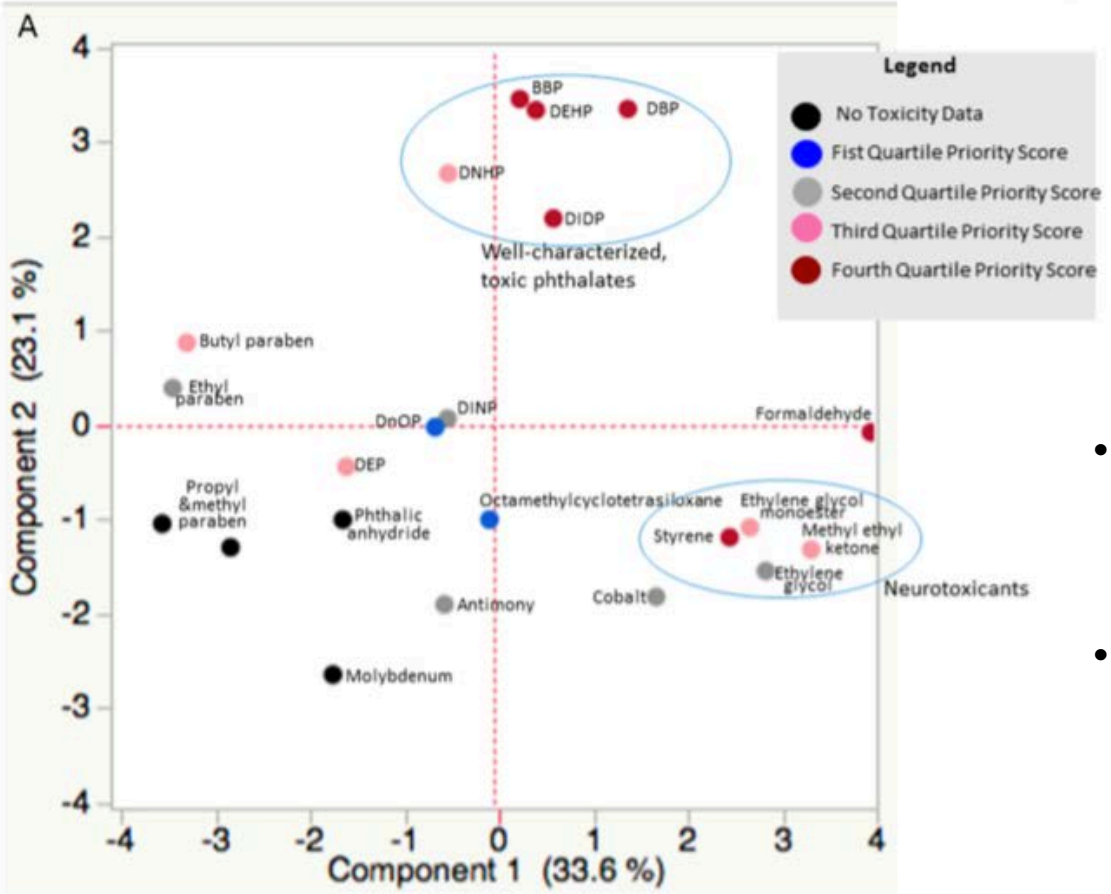
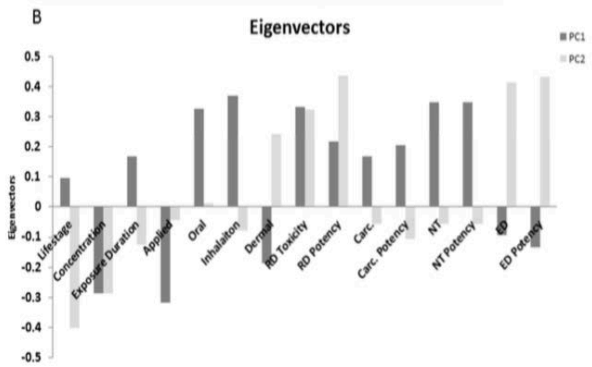
High Priority Chemicals

Chemicals that cluster together share toxicities.





- 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.

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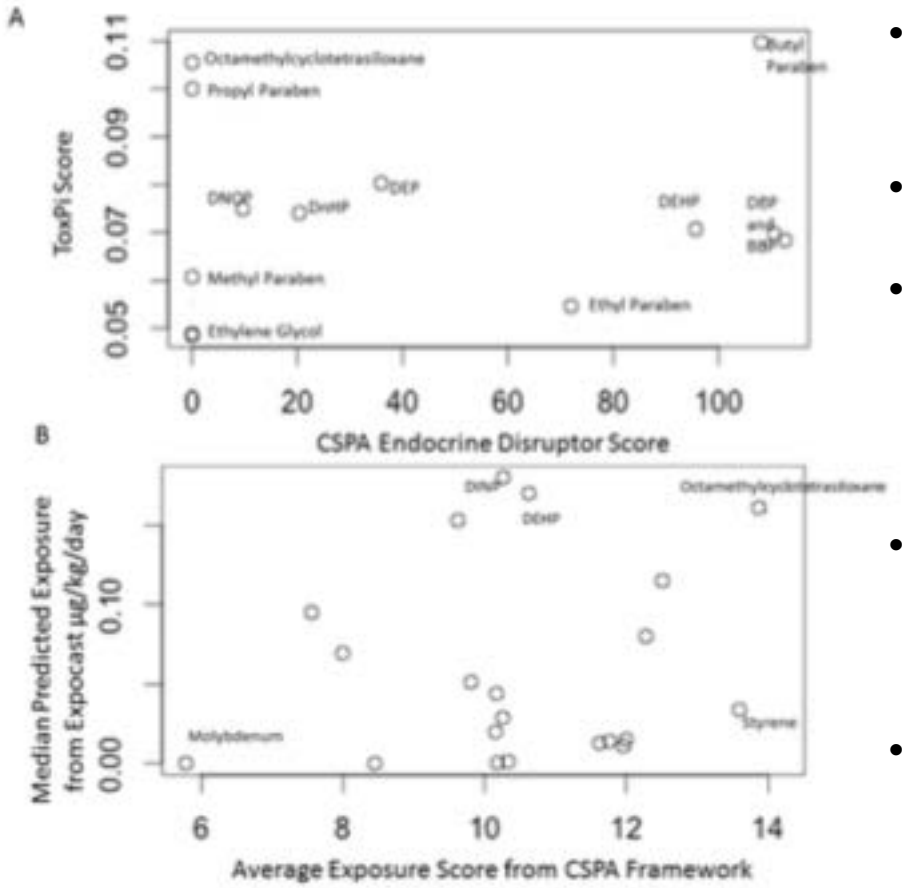
Comparison with other prioritization frameworks



- 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
- Octamethylcyclotetrasiloxane and propyl paraben, score relatively high using ToxPi but are not classified as endocrine disruptors using the CSPA framework
- Octamethylcyclotetrasiloxane has a relatively high ExpoCast predictions and score higher using the CSPA framework for average exposure scores.
- The phthalates DINP and DEHP, have higher exposure predictions from ExpoCast than exposure scores using the CSPA framework.

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Applications

- Overall, this framework allows for the ranking of chemicals in products that may be hazardous to children's health.
- Integrates information from chemical and product features
- Can be used in conjunction with other prioritization frameworks (e.g. ToxCast, ExpoCast)
- Allows for the identification of concerning chemical-product combinations with strong supporting evidence of toxicity and those with high exposure potential, but less well-characterized health outcomes

Caveats and Future Work

- Framework is dependent on extant data from
  - In some cases, existing data was limited
- CSPA is still in a phase-in process with the largest manufacturers reporting their results, but requirements for smaller manufacturers are still being phased in
- Achieve a balance between high throughput and high content for framework and interpretation
  - As of January, 2016, there were over 33,000 records in the CSPA database

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