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Webinars

- Series of scientific webinars that provide a forum for discourse on scientific issues.
- Live and On-Demand
- Case Conferences
  Journal Clubs
  Grand Rounds
- CE Available

Online Courses

- Evidence-based online courses on a variety of children's environmental health topics.
- Interactive and Self-Paced
- CE Available

Resource Catalog

- Fact sheets, journal publications, reports, and other resources for parents, community members, patients and healthcare professionals
- Topics included:
  Air Quality, Pesticides, Natural Disasters, BPA, Mold, Lead, Mercury

Prioritizing Toxic Chemicals in Children's Consumer Products

Elaine Faustman and Marissa Smith
Center for Child Environmental Health Risks Research
Department of Environmental and Occupational Health Sciences,
University of Washington

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Learning Objectives

- Summarize the regulation of chemicals in consumer products in Washington State
- Identify the benefits and shortcomings of Washington's approach
- Summarize the Children's Safe Product Act and identify the types of data required to be reported
- Discuss the toxicity and exposure related concerns relevant to prioritizing chemicals in consumer products
- Assess the Toxic Substances Control Act Reform's impact on children's consumer product regulation

A Chemical World

- ~85,000 chemicals found in consumer products sold or manufactured in the US (EPA)
  - Small fraction evaluated for risks to human health
  - Associated with increased risk of:
    - cancer
    - neurodevelopmental delays
    - obesity
    - infertility and other reproductive health problems
- Children vulnerable to exposures because they interact with products in unique ways and have developing organ systems

Burden of Disease from Environmental Chemicals

- ~5-20% of neurobehavioral disorders attributable to environmental chemical exposures
- $9.2 billion = US annual cost for environmentally attributable neurobehavioral disorders
- Total costs were equivalent to 2.8% of United States healthcare spending
- Reducing exposure can prevent disease!

Landrigan et al. 2002

Toxic Chemicals Found in Consumer Products

- Formaldehyde- Carcinogen
- Styrene- Carcinogen, neurotoxicant
- Phthalates- Endocrine Disruptors, Reproductive and Developmental Toxicants
- Toxic Metals- Carcinogens, neurotoxicants
- Parabens- Endocrine Disruptors

Regulations in US

The Consumer Product Safety Improvement Act of 2008

- Lead
  - 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 and butyl benzyl phthalates:
  - Concentrations 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 phthalates:
  - 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.

Regulations in Washington

- Total phthalates- no greater than 1000ppm
  - Eliminates some problems with regrettable substitutions
  - Shared toxic impacts- especially on the reproductive system
  - A 30 pound crib mattress can contain up to ½ ounce of phthalates combined (up to 3 oz by federal limits)
  - Federal law preempts state regulations for some children's products, but not all
- Cadmium- no greater than 40ppm

Cadmium in Children's Jewelry

- Purchased 159 items of inexpensive all-metal children's jewelry and metal-based jewelry with plastic components.
- Cadmium was detected in 16% (26/159)
- High levels of cadmium−98.4%, 93.1%, 53.4%, and 39.7%− were detected in four necklaces sold along with children's dresses.
- One of these products had high levels of cadmium (93.1%) and lead (846 ppm).

WA Department of Ecology. 2015
https://fortress.wa.gov/ecy/publications/documents/1603007.pdf

Department of Ecology's approach to reducing toxic exposure

Averting toxic exposures and avoiding future costs is the smartest, cheapest and healthiest approach

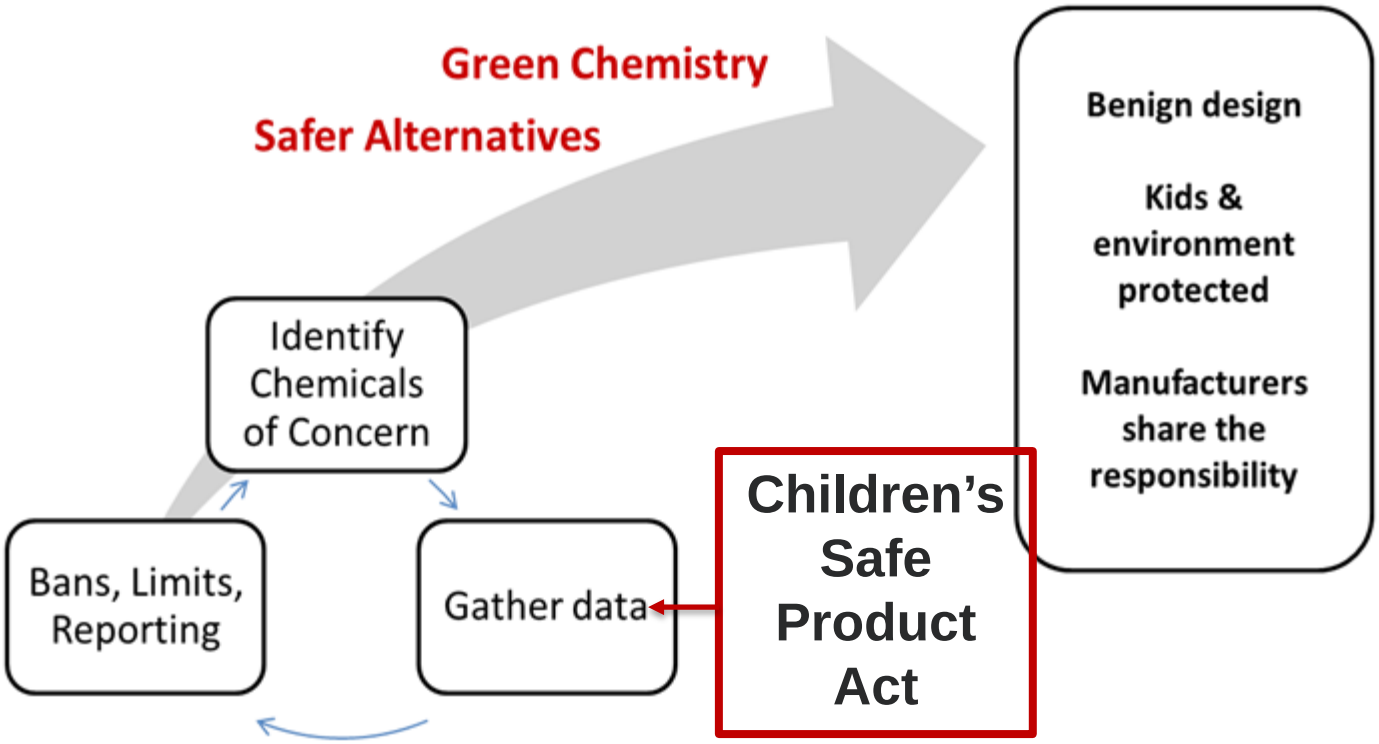


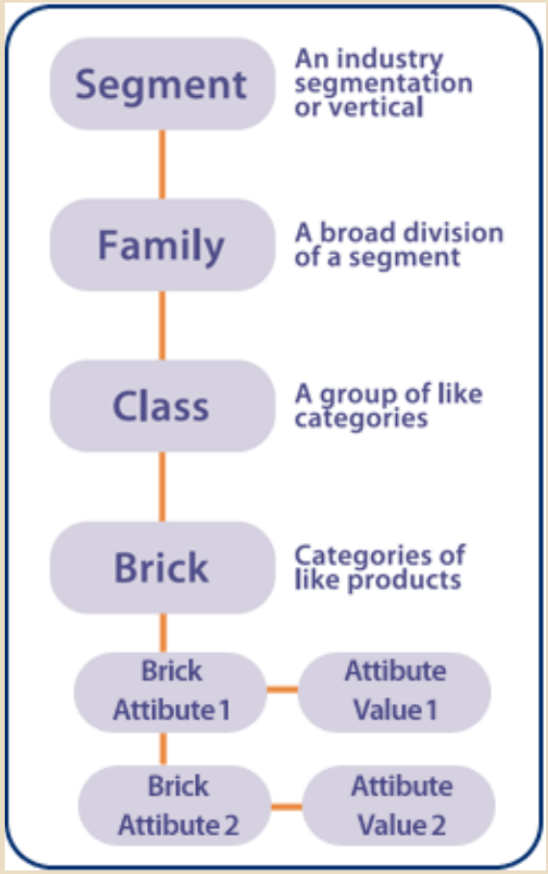
Figure- Grice 2014

Children's Safe Product Act (CSPA)

- Passed in 2008 in Washington State
- Requires manufacturers report the presence of 66 Chemicals of High Concern to Children in children's products sold in WA state
  - Target age group (under 3yo, 3yo 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

Children's Safe Product Act (CSPA)



Segment	Example bricks
Arts/crafts/needlework	Artists paints/dyes, Artists pastels/crayons, Jewelry craft materials, Sand art supplies
Baby care	Pacifiers/teething rings, Baby bath safety products, Baby changing mats, Baby furniture/transportation/safety
Beauty/personal care	Cosmetic aids/accessories, Fragrances, Hair-shampoo, Dental cleansing, Lip Balms
Clothing	Handwear, Headwear, Skirts, Socks, Trousers/Shorts, Sleepwear Variety Packs
Footwear	Athletic footwear, Boots, Shoes
Household	Cushions, Bed sheets/valances, Pillow cases
Personal accessories	Anklets, Earrings, Necklaces, Rings, Tiaras
Toys/games	Board games, Practical jokes, Puppets, Developmental/educational toys, Outdoor games, Toy vehicles, Role play – kitchen toys

Chemicals of High Concern to Children (CHCC)

- Identification of chemicals based on a three phase process based on:
  - Toxicity-Carcinogenicity, Reproductive and Developmental Toxicity and Endocrine Disruption
  - Evidence of the chemical in children's products
- Done in consultation with the Department of Health and UW's Pediatric Environmental Health Specialty Unit
- Data sources included:
  - International Agency for Research on Cancer (IARC)
  - U.S. National Toxicology Program
  - U.S. Environmental Protection Agency
  - European Commission, Joint Research Center, Institute for Health and Consumer Protection
  - State of California List of Proposition 65 Chemicals

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	

Presentation Focus

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

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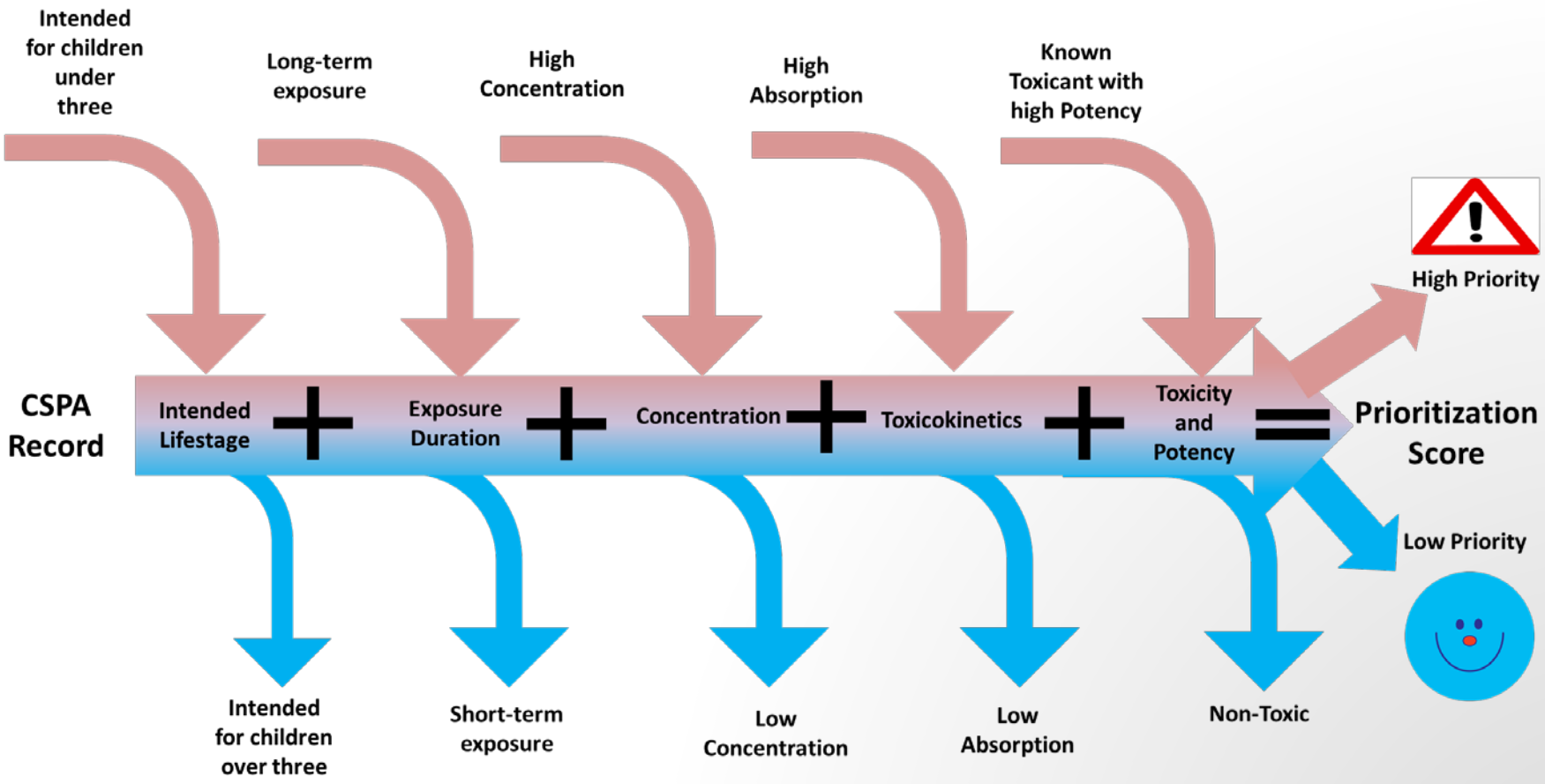
How do we integrate this information?

- 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

Do you care more about cobalt in a shoe or DEHP in a shirt?

What Matters in Prioritizing CSPA Chemicals?



Smith 2015

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

Accessibility: Inaccessible=1, accessible=3

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
Applied Directly to Skin
Exposure Duration
Exposure Routes
Absorption

LogP
Solubility
Vapor Pressre
Certainty of Toxicity
Potency of Toxicity

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


Smith 2012

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]

Smith et al. 2016. IJPHR. 13(4)

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 1	Score 2	Score 3	Basis
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

Smith et al. 2016. IJPHR. 13(4)

Variable Scoring: Toxicity Endpoints and Potency

Toxicity Endpoints and Data Sources

- **Carcinogenicity:** IARC, Prop 65, Global Harmonization Standard, EPA IRIS
- **Reproductive and Developmental Toxicity and Endocrine Disruption:** REACH Existing Substances, Prop 65 and Global Harmonization Standard
- **Neurotoxicity:** Grandjean and Landrigan et al. 2014 was used to identify neurotoxicants.

European Union Approaches: Existing Substances Prioritization List

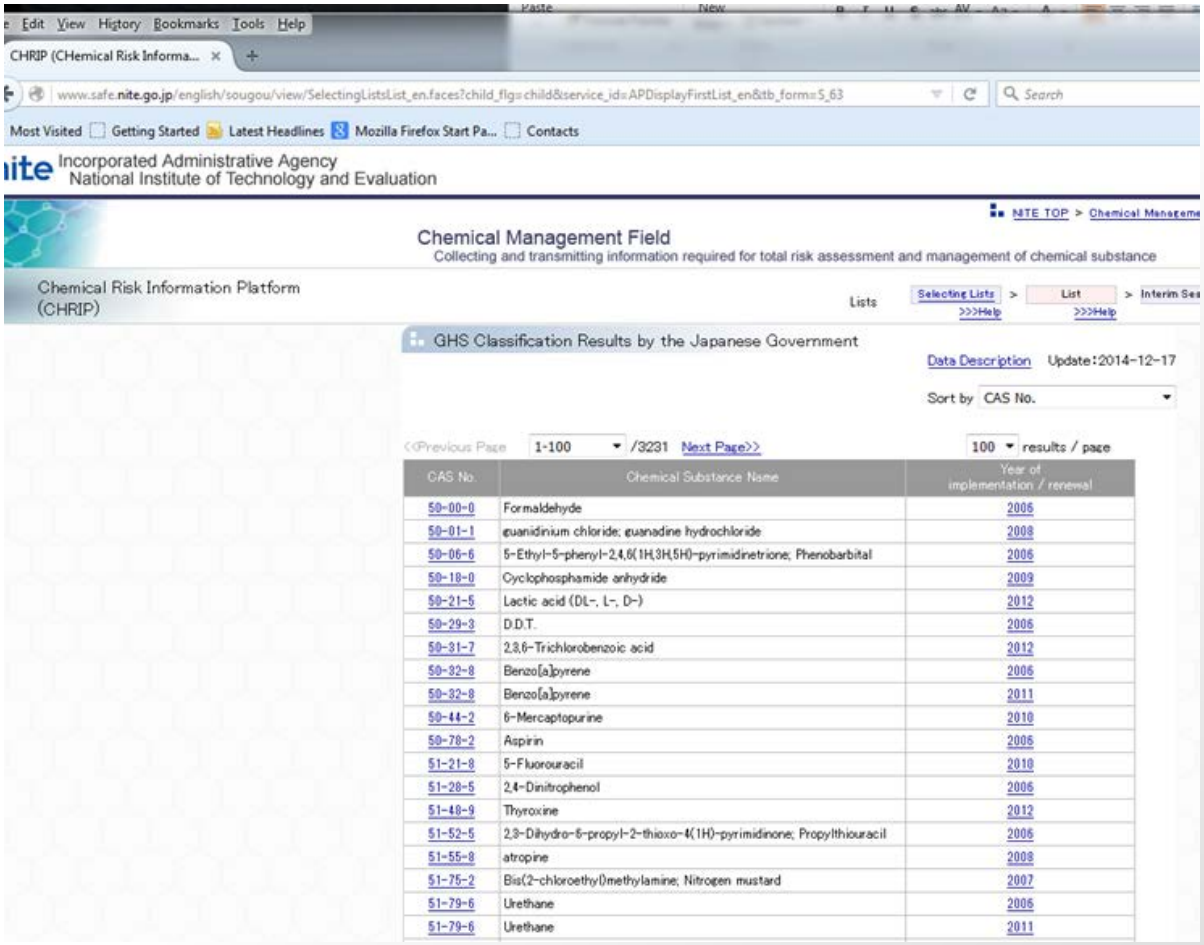
- Based on the strength of evidence for endocrine disruption, chemicals were assigned to one of three categories:
  - **Category 1**
    Evidence of endocrine disrupting activity in at least one species using intact animals
  - **Category 2**
    At least some in vitro evidence of biological activity related to endocrine disruption
  - **Category 3**
    No evidence of endocrine disrupting activity or no data available.
- The results of these studies are compiled in a database.
  - http://ec.europa.eu/environment/chemicals/endocrine/strategy/substances_en.htm#priority_list

International Agency for Research on Cancer

- *IARC Monographs* identify environmental factors that can increase the risk of human cancer.
- Include chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and lifestyle factors.
- Classified in Groups 1-4 based on evidence of cancer in human and animals.
  - Group 1: Agent is carcinogenic to humans
  - Group 2: Agent is possibly/probably carcinogenic to humans
  - Group 3: Agent is not carcinogenic to humans
  - Group 4: In sufficient information to determine carcinogenicity

Global Harmonized System for Hazard Communication

- Internationally harmonized chemical information
- United Nation, 2003
- Japanese National Institute of Technology Evaluation Interface -CHIRP



CAS No.	Chemical Substance Name	Year of implementation / renewal
50-00-0	Formaldehyde	2006
50-01-1	guanidinium chloride; guanadine hydrochloride	2008
50-06-6	5-Ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione; Phenobarbital	2006
50-18-0	Cyclophosphamide anhydride	2009
50-21-5	Lactic acid (DL-, L-, D-)	2012
50-29-3	D.D.T.	2006
50-31-7	2,3,6-Trichlorobenzoic acid	2012
50-32-8	Benzo[a]pyrene	2006
50-32-8	Benzo[a]pyrene	2011
50-44-2	6-Mercaptopurine	2010
50-78-2	Aspirin	2006
51-21-8	5-Fluorouracil	2010
51-28-5	2,4-Dinitrophenol	2006
51-48-9	Thyroxine	2012
51-52-5	2,3-Dihydro-6-propyl-2-thioxo-4(1H)-pyrimidinone; Propylthiouracil	2006
51-55-8	atropine	2008
51-75-2	Bis(2-chloroethyl)methylamine; Nitrogen mustard	2007
51-79-6	Urethane	2006
51-79-6	Urethane	2011

California Prop 65

- In 1986, California voters approved an initiative to address their growing concerns about exposure to toxic chemicals.
- Proposition 65 requires the State to publish a list of chemicals known to cause **cancer or birth defects or other reproductive harm.**
- List must be updated at least once a year
  - Includes approximately 800 chemicals

EPA IRIS

- Integrated Risk Information Systems
- IRIS Toxicity Values
  - Oral Reference Dose
  - Inhalation Reference Concentration
  - Cancer Descriptions
    - Carcinogenic to humans
    - Likely to Be Carcinogenic to Humans
    - Suggestive Evidence of Carcinogenic Potential
    - Inadequate Information to Assess Carcinogenic Potential
    - Not Likely to Be Carcinogenic to Humans
  - Oral Slope Factor: is an estimate of the increased cancer risk from oral exposure to a dose of 1 mg/kg-day for a lifetime. The OSF can be multiplied by an estimate of lifetime exposure (in mg/kg-day) to estimate the lifetime cancer risk.
  - Inhalation Unit Rise
- 570 Chemical Records

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.

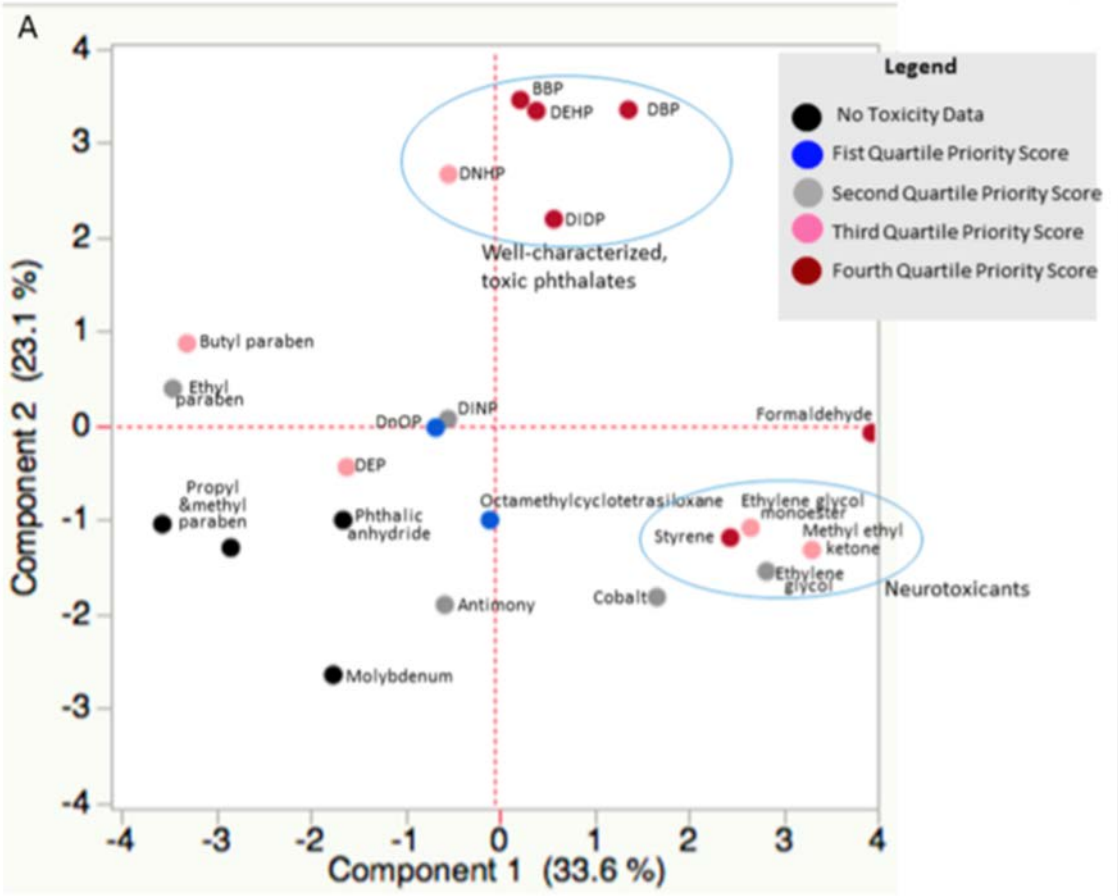
High Priority Chemicals

- Formaldehyde, styrene and dibutyl phthalate have the highest total priority scores due to high toxicity and exposure scored
- DEHP, butyl benzyl phthalate, diisodecyl phthalate and butyl paraben also have high scores for toxicity and exposure

Smith et al. 2016. IJPHR. 13(4)

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 (bottom circle)
- Phthalates that are well-characterized endocrine disruptors and reproductive and developmental toxicants cluster together as well (top circle)

Smith et al. 2016. IJPHR. 13(4)

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)

Applications

- 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
- Prioritize chemical for closer monitoring, regulation, alternatives research, etc…

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 September, 2016, there were over 44,000 records in the CSPA database

Toxic Substances Control Act- Reform

- In June, 2016 President Obama signed the Frank R. Lautenberg Chemical Safety for the 21st Century Act, for reforming the Toxic Substances Control Act (TSCA) originally passed in 1976.
- Because TSCA was so outdated, many states had regulated chemicals in consumer products on their own
- How will this affect CSPA?
  - Reporting frameworks are still okay at the state level
  - More stringent rules in WA could be changed if EPA takes action on these chemicals (phthalates, cadmium)

Introduction to Toxic Substances Control Act

- The Toxic Substances Control Act (TSCA) of 1976 provides EPA with authority to require reporting, record-keeping and testing requirements, and restrictions relating to chemical substances and/or mixtures.
- Certain substances are generally excluded from TSCA, including, among others, food, drugs, cosmetics and pesticides
- Addresses the production, importation, use, and disposal of specific chemicals including polychlorinated biphenyls (PCBs), asbestos, radon and lead-based paint.
- The Office of Pollution Prevention and Toxics (OPPT) manages programs under the Toxic Substances Control Act and the Pollution Prevention Act.
- Under these laws, EPA evaluates new and existing chemicals and their risks, and finds ways to prevent or reduce pollution before it gets into the environment.

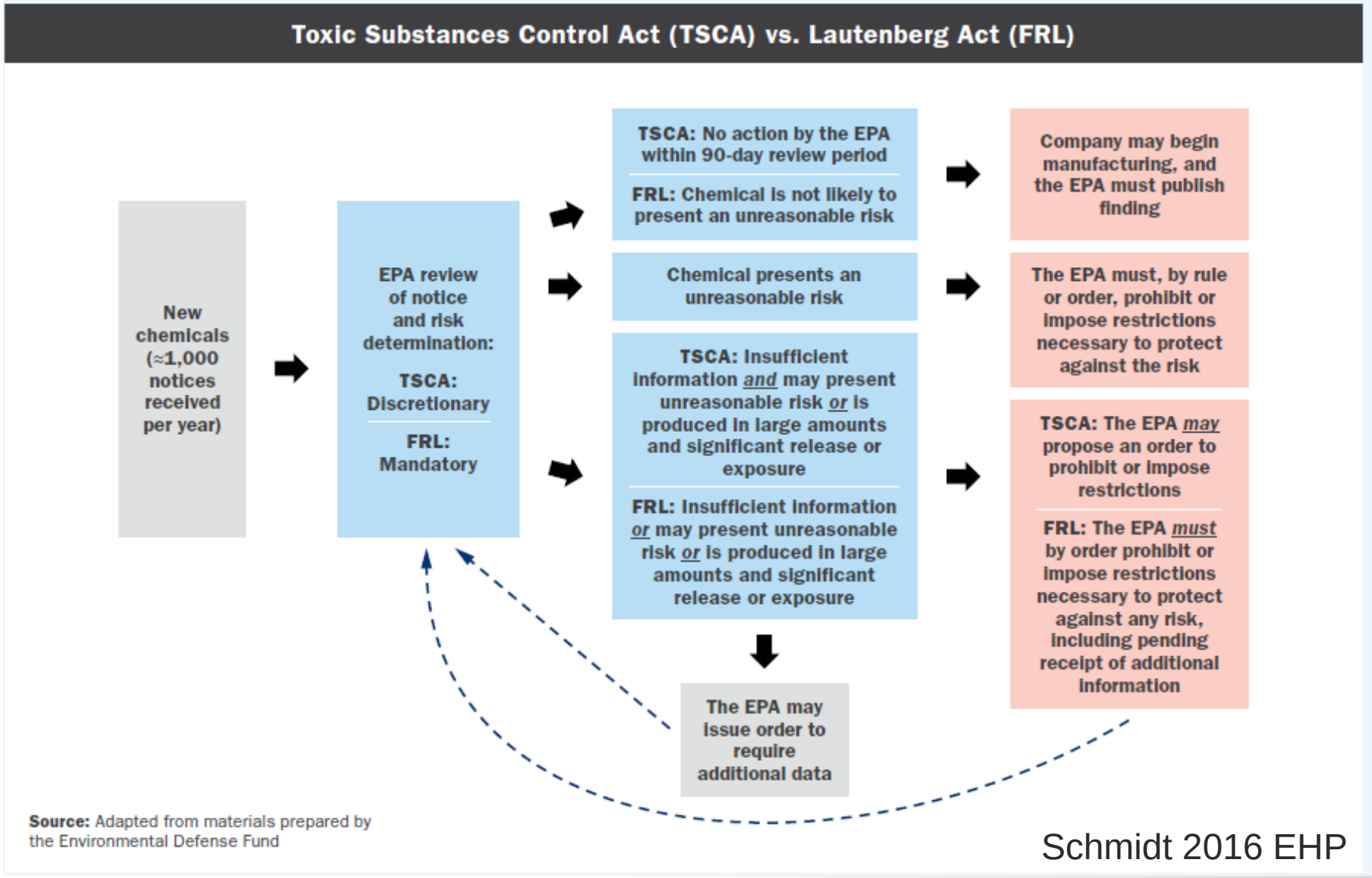
https://www.epa.gov/laws-regulations/summary-toxic-substances-control-act

Previous Weaknesses of TSCA

- No toxicity testing requirements or minimum datasets
- Without evidence of harm, chemicals were viewed as safe
- EPA was forced to rely on heavily on prediction models
- EPA could only require testing when it could show risk

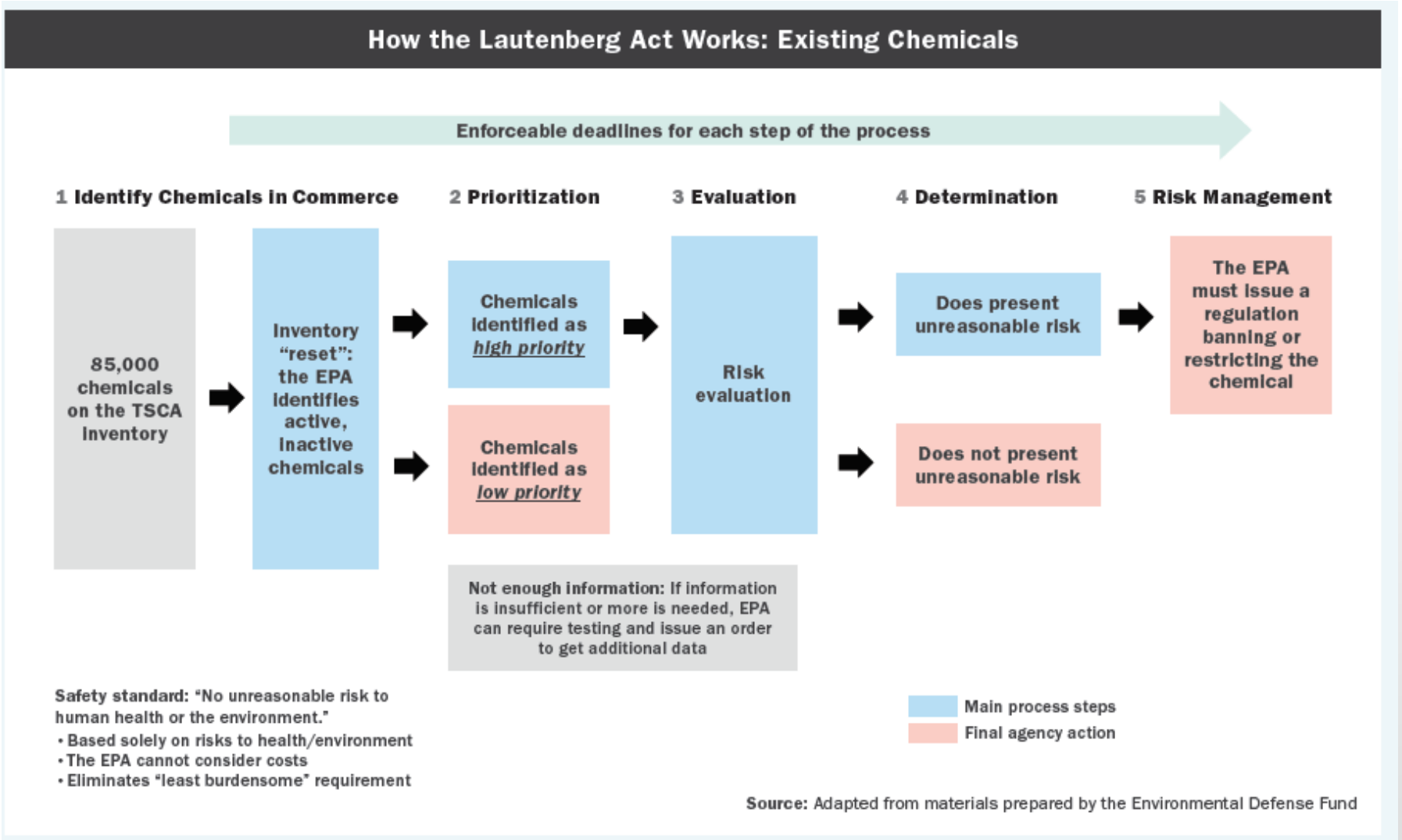
https://www.epa.gov/laws-regulations/summary-toxic-substances-control-act

Toxic Substances Control Act Compared to Lautenberg Act



Schmidt 2016 EHP

Toxic Substances Control Act Compared to Lautenberg Act



Schmidt 2016 EHP

Other Children's Safe Product Acts

- Other State programs:
  - Oregon- in progress, very similar to WA, contains an enforcement element
  - California- did not pass
  - Vermont- Will start reporting in January 2017, working on product level reporting
  - Main- Active, no data available yet
  - Minnesota- in progress
- Europe: Norway and Sweden (since 1970s)- data is not publicly available
- Unique features of WA:
  - Publicly available database since 2012
  - Active follow-up with Ecology's product testing program (Cadmium in jewelry results)

Conclusions

- CSPA mandates chemical of concern reporting and limits concentrations of phthalates and cadmium in children's products
- Department of Ecology conducts an active monitoring of children's products in tandem with the manufacturers' reports
- Information on chemical concentration, toxicity, potency and product exposure factors can be used to prioritize chemicals in children's products
- Dibutyl phthalate, styrene and formaldehyde were the highest priority chemicals found in this analysis
- These results can be used to guide future monitoring and enforcement efforts

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Image Citations

Slide 2: Image: https://www.pexels.com/photo/child-holding-unicorn-toy-6191/ Free for personal and commercial use

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Slide 10- Grice et al. 2014

Slide 16- Smith 2012

Slide 17- Smith 2015

Slide 19- Grice 2015

Slide 21- Smith 2012

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