Case Studies for Using in vitro and in silico Models to Prioritize Chemicals of Concern in Children's Products

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Toxic Chemicals Found in Consumer Products

- Formaldehyde- Carcinogen
- Styrene- Carcinogen, neurotoxicant
- Phthalates- Endocrine Disruptors, Reproductive and Developmental Toxicants
- Bisphenol A-Endocrine Disruptors, Reproductive and Developmental Toxicants
- Parabens- Endocrine Disruptors
- Toxic Metals- Carcinogens, neurotoxicants
  - Cadmium in Jewelry
- Silver or Cadmium nanoparticles
  - Antimicrobial properties

Children's Products Reporting Frameworks

Reporting frameworks for chemicals in consumer products are growing more common at both national and international levels.

Reporting Requirement	State/Location	Enacted/Data Collection	Accessible Database
Children's Safe Product Act	WA	2008/2011	Yes
Toxic Free Kids Act	OR	2015/2018	Summer, 2019
S.239	VT	2014/2017	Yes
Safer Chemicals in Consumer Products	ME	2015/2017	Not Yet
California Safe Cosmetics Program	CA	2005	Yes
CPCAT/CP DAT	National-EPA	2012-2013 and 2017	Yes
Interstate Mercury Reporting	NY, VT, MA, RI, LA, ME, CN, NH	2001 (NH) by 2011 (5 states)	Yes
Norwegian Product Registry	Norway	1982	No
Swedish Product Registry	Sweden	1972	Yes

Engineered Nanomaterials in Children's Products

- FDA and CPSC do not specifically regulate ENM in children's products
- TSCA (Frank Lautenberg Chemical Safety for Sustainability Act) does not specifically call out nanomaterials. But discusses "molecular identity"
- Prioritization for regulation generally is based on inclusion in authoritative lists or hazard identification

Drive for Safer Alternatives

- Chemicals of high concern to children are commonly found in children's consumer products
- States are passing regulations that require manufacturers to report concentrations of toxic chemicals in publicly available databases
- States are regulating the concentrations of toxic chemicals in children's consumer products
- Consumers are demanding toxic-free children's products
  - As BPA-Free and Phthalate-free products are introduced, what are they being replaced with?

Alternatives Assessment Data Needs

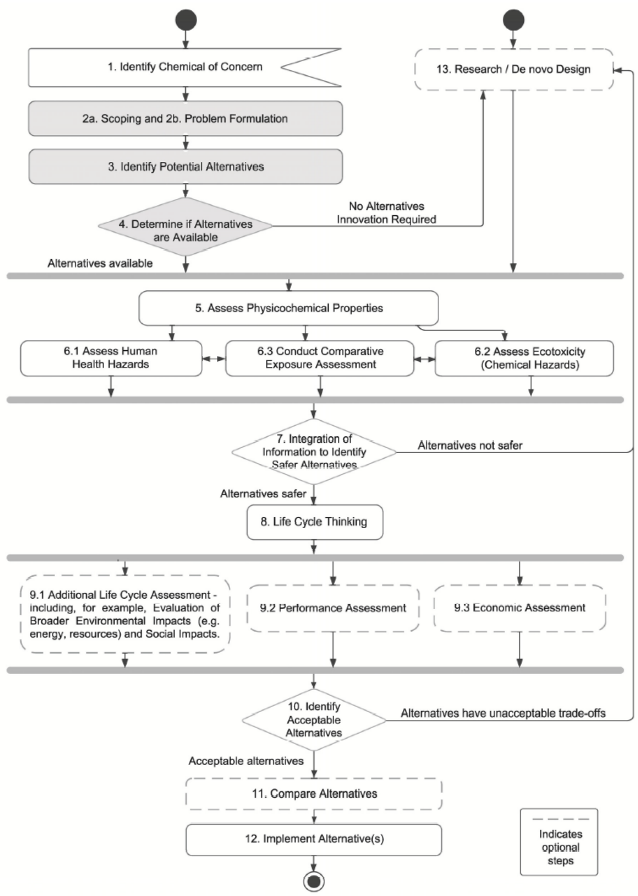
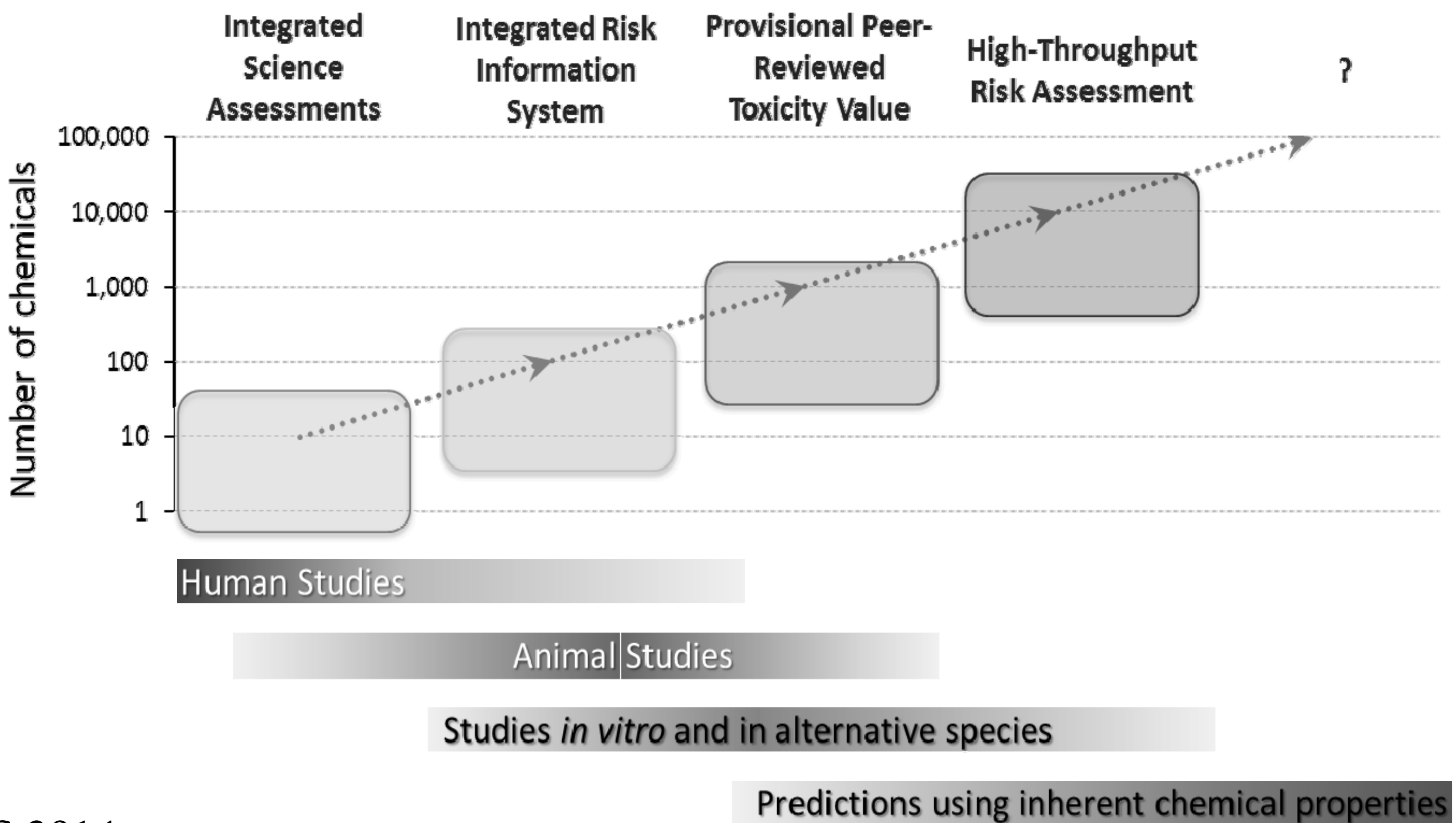


FIGURE 4-1 Committee's framework highlighting scoping, problem formulation, and identification of potential alternatives.

- Alternatives Assessments require toxicity and exposure data at multiple levels
- In contrast to a traditional risk assessment, information about both the conventional and alternative chemicals is needed
- Information needed to:
  - Identify alternative
  - Assess toxicity
  - Assess exposure
  - Assess lifecycle impacts
  - Assess ecotoxicity
  - Determine functionality
  - Assess social and economic implications

NAS Alternative Assessment 2014

Data Availability



NAS 2014

Case Study: Phthalate, Paraben and Bisphenol A Alternatives

Goal: To determine whether in vitro and in silico data sources increase data availability for alternatives assessments for phthalates, parabens and BPA.

Step 1
Identification of case studies
Focus on toxic chemical found in children's consumer products with available alternatives

Step 2
Identification of alternatives
Peer Reviewed Publications and Industry Reports[10, 16, 18, 19]

Step 3-5
Hazard Assessments
Authoritative Lists ECHA[21] & GHS[22]
In vivo Data ComTox Chemistry Dashboard[26]
In vitro Data ToxPi[25]

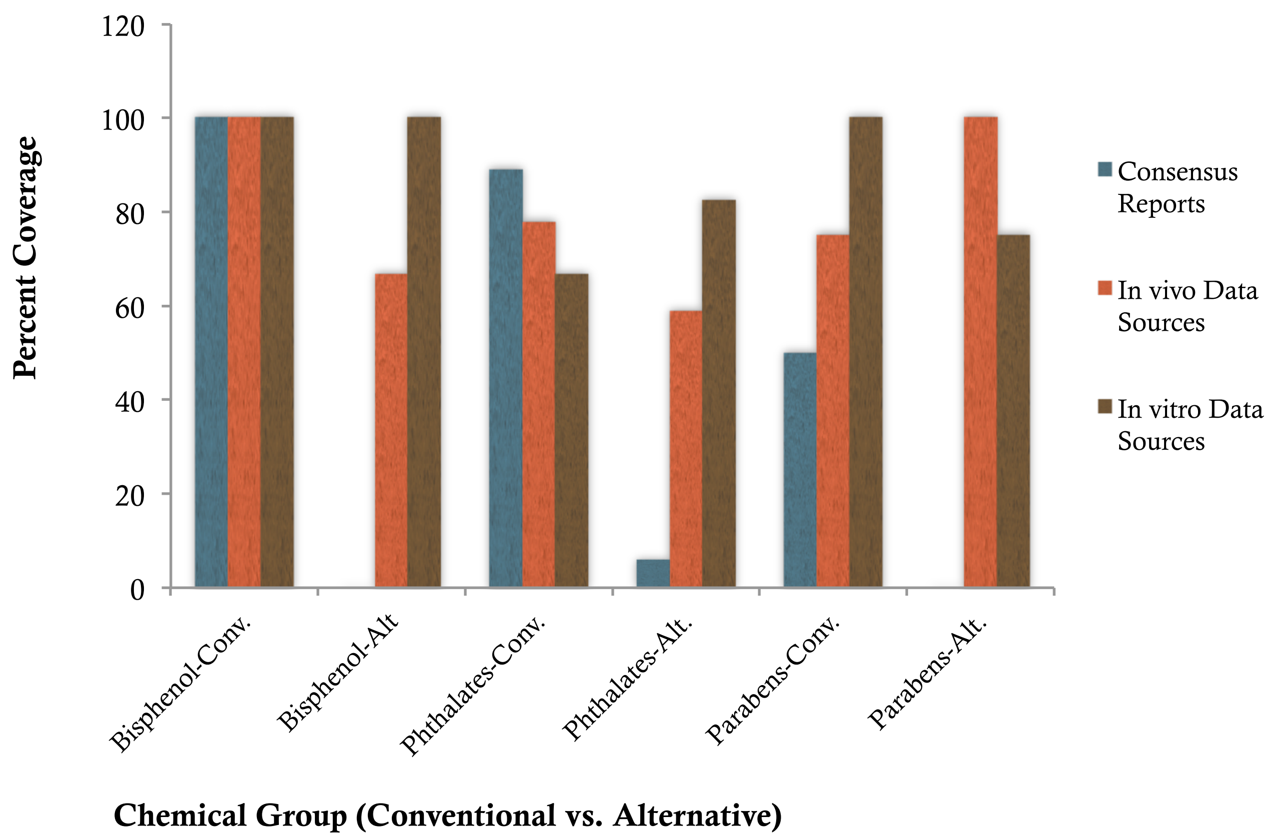
Step 6
Exposure Comparison
ExpoCast[27]

Step 7
Functional Comparison
FUse[28]

Analysis
Research Questions:

1. Does the coverage of alternative vs. conventional chemicals characterized vary by hazard assessment type?
2. Does adding in vitro data improve our understanding of alternative chemicals' potential hazard?
3. Are there differences in predicted exposures between alternative and conventional chemicals?
4. Are there differences in the predicted functions of conventional and alternative chemicals

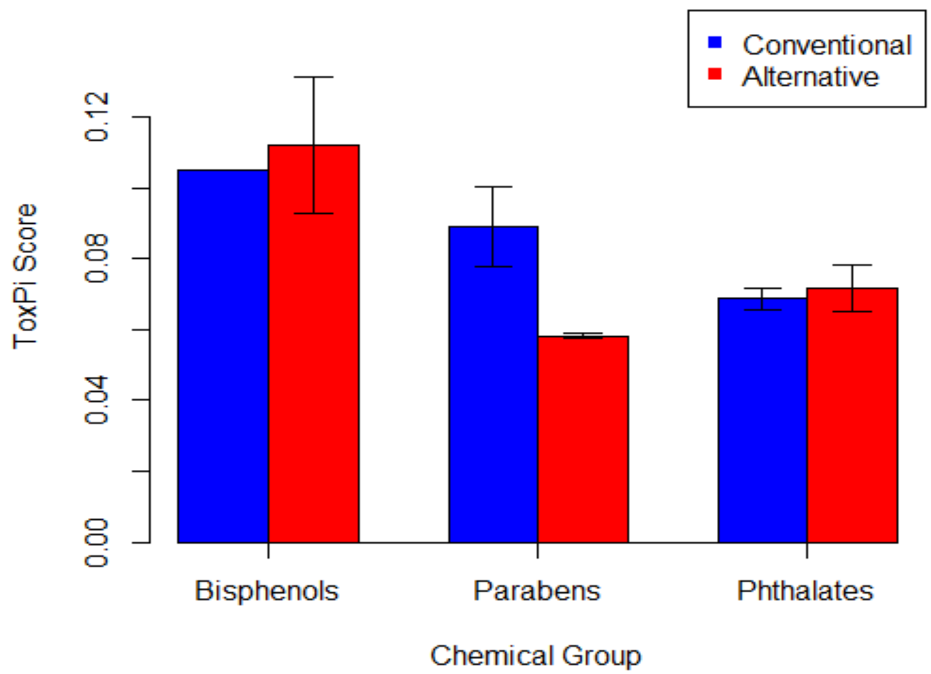
Percent of conventional and alternative chemicals found in consensus reports, in vivo and in vitro databases



Compared to consensus reports, in vitro and in vivo data sources were more likely to include alternatives

For phthalates and bisphenols, in vitro data bases included more alternatives than in vivo databases

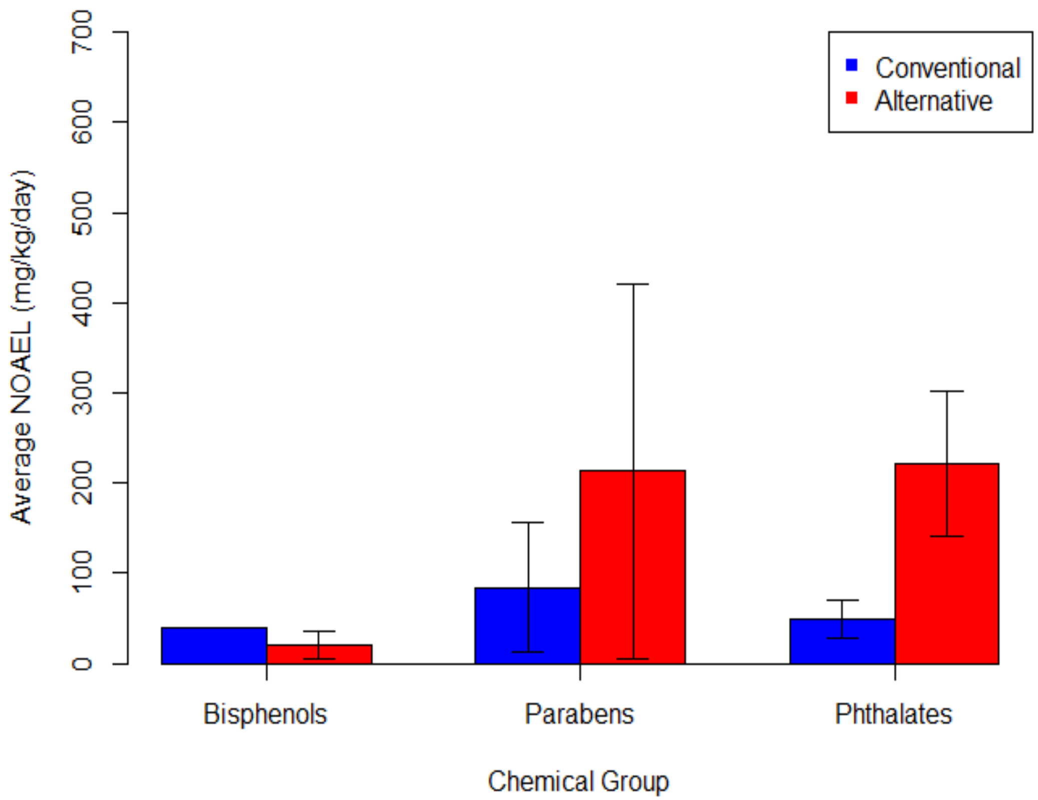
Comparison of the average ToxPi score for conventional and alternative chemicals



For all three case examples the average ToxPi scores were similar between conventional chemicals and alternative chemicals.

Error bars represent standard error.

Average NOAELs for Conventional and Alternative Chemicals

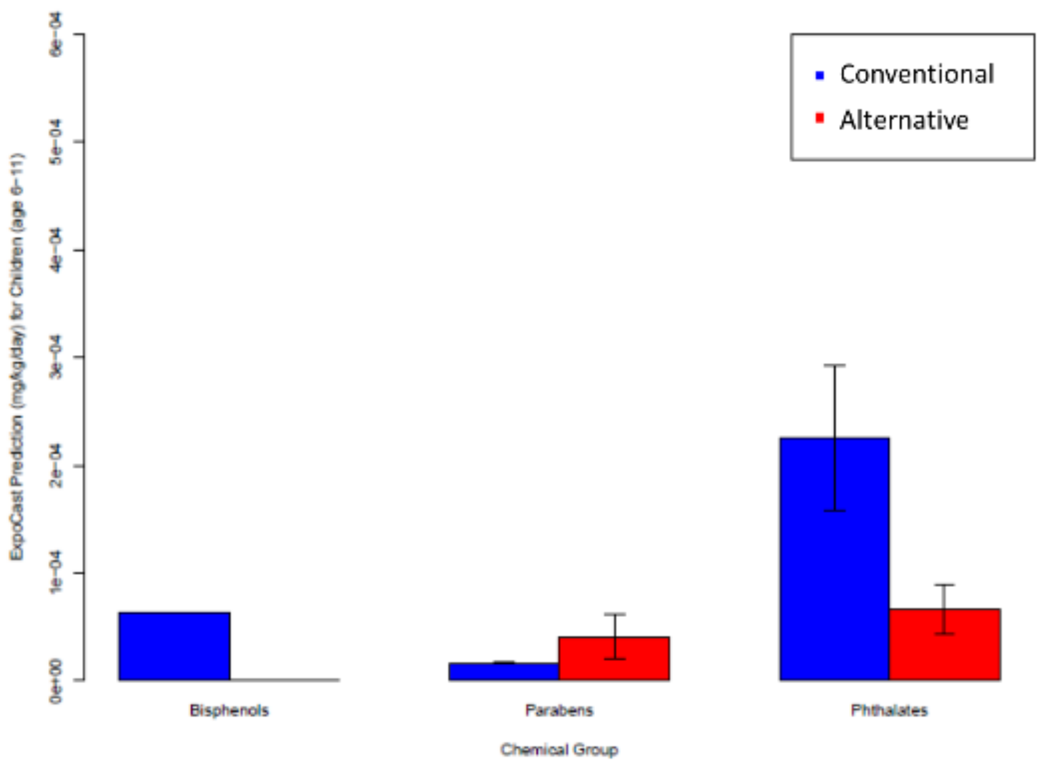


For all chemical groups the average NOAEL is lower among conventional chemicals than alternatives.

This indicates that based on the animal data available, alternative chemicals may be on average less hazardous than conventional chemicals, for these three chemical groups.

Error Bars represent standard error.

The average ExpoCast Prediction for Alternative and Conventional Chemicals



For bisphenols and phthalates, conventional chemicals have higher predicted exposure than alternatives.

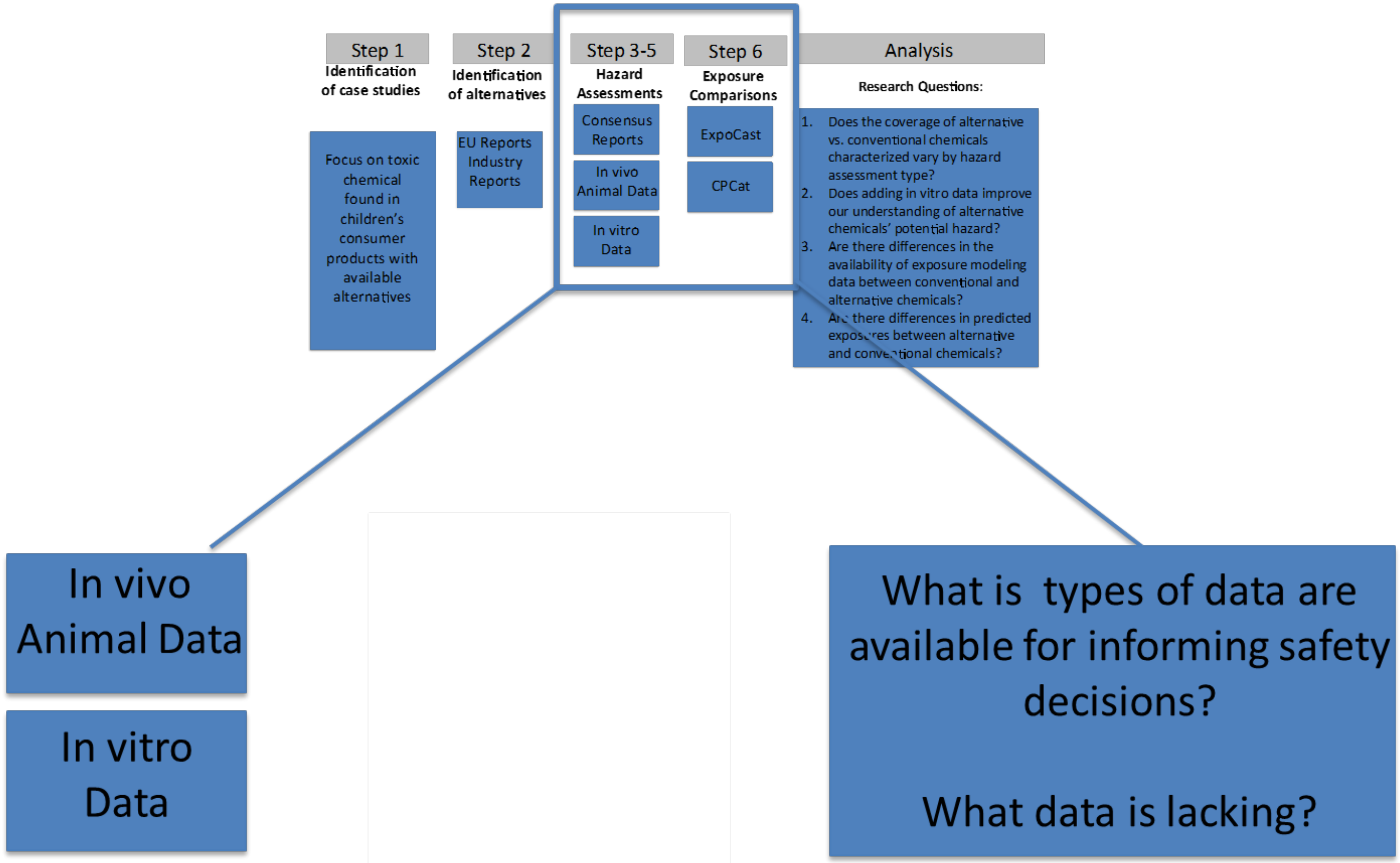
For parabens, alternative and conventional chemicals have similar exposure predictions

Error Bars represent standard error

Putting Safer Alternatives in Context

- Paraben alternatives were classified as less toxic than conventional chemicals using both in vitro and in vivo databases.
  - All paraben alternatives were found in EPA's Safer Chemical Ingredients list
- If we use the ratio of the ToxPi scores for paraben conventional and alternative chemicals as an anchor, we can hypothesize about the impacts of higher concentrations of alternatives being used
  - In this case 1.54 times higher concentrations may still have positive public health impacts

Case Study: Engineered Nanomaterials



EMN Hazard Assessment- In vivo

- Critical Studies for AgNP Hazard Assessment

Rodent Study	AgNP Type	Species, Strain, Sex,	Route of Exposure	Animals/ Dose Group	Exposure Concentration/ Duration
Sung 2009	18-19 nm Uncoated	Sprague Dawley rat Male and Female	Inhalation	10	0, 49, 133, 515ug/m^3 6hr/day, 5/day/week 13 weeks
Sung 2008	18-19 nm Uncoated	Sprague Dawley rat Male and Female	Inhalation	4	0, 49, 133, 515ug/m^3 6hr/day, 5/day/week 13 weeks

Derivation of an Occupational Exposure Limit (OEL)

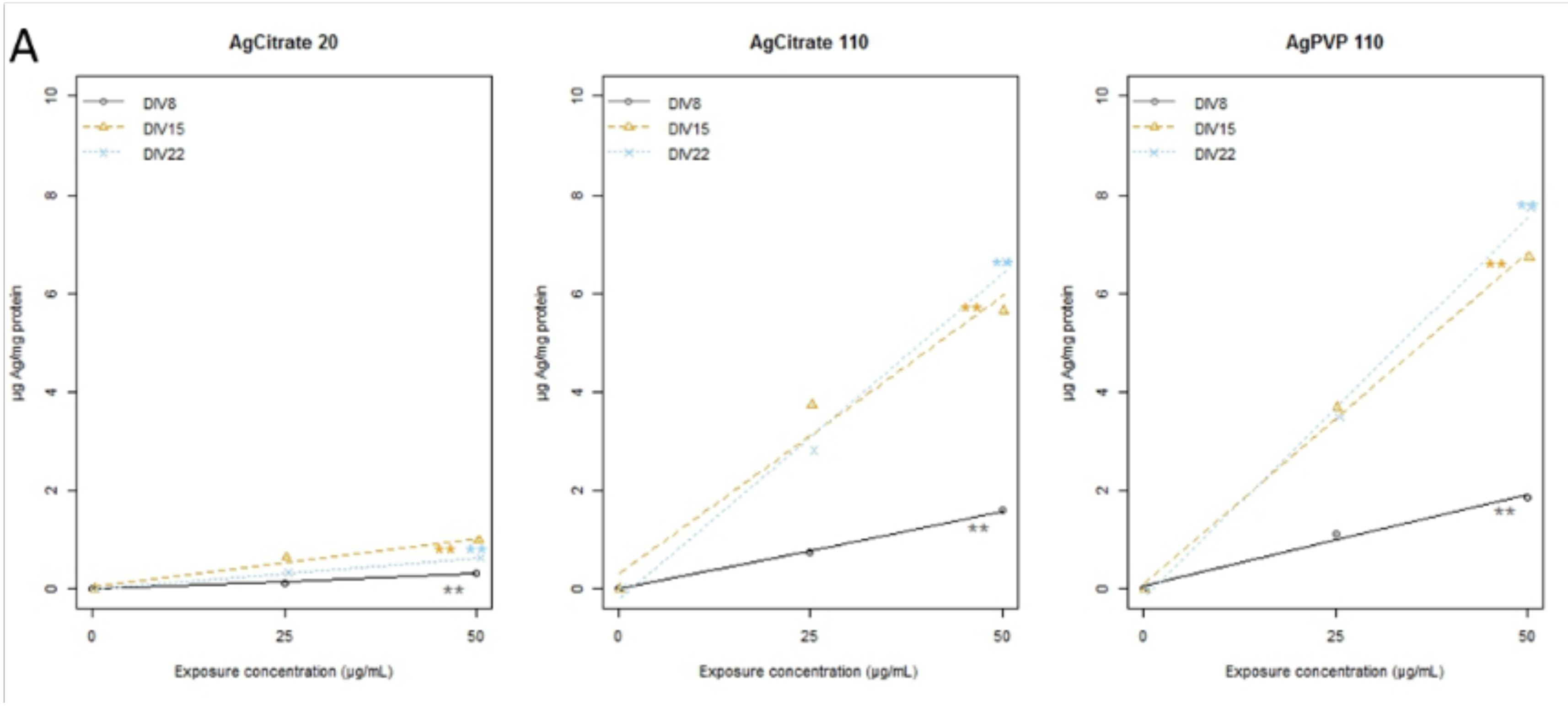
$$HEC\_BMCL = \frac{Rat\ BMCL}{\left(\frac{Ventilation\ rate\ human}{Ventilation\ rate\ rat}\right) x \left(\frac{Deposition\ rate\ human}{Deposition\ rate\ rat}\right) x \left(\frac{Clearance\ rate\ human}{Clearance\ rate\ rat}\right) x \left(\frac{Alveolar\ Surface\ Area\ rat}{Alveolar\ Surface\ Area\ human}\right)}$$

- The proposed OEL of 0.19 μg/m^3 is expected to prevent liver and lung damage from AgNPs exposure by inhalation in workers.
- The current OELs for silver dust and soluble silvers (micro-sized particles) are 100 and 10 μg/m^3, respectively. This level will not protect against adverse health effects from silver nanoparticles.
- Challenges:
  - Relevant exposure data- these assessments were only for inhalation, some ingestion may also occur
  - Lack of in vitro data for extrapolation

Weldon et al. 2016

Using In vitro models (human neuroprogenitor cells) to study dosimetry

Effect of developmental stage of exposure on Ag dosimetry



More Ag associated with cultures at DIV 15 and DIV 22 for all particles

Weldon et al. 2016

Conclusions

1. In vitro databases increase coverage of toxicological data for alternative chemicals that may soon be replacing toxic chemicals in children's products relative to authoritative lists and reports.

2. While phthalates and Bisphenol A alternatives had similar toxicities, in vivo and in vitro data suggests that paraben alternatives may be safer options. All paraben alternatives were included in EPA's Safer Chemical Ingredients List, while only 2 out of 17 of the phthalate alternatives and no bisphenol A alternatives were included.

3. Exposure to conventional chemicals is currently predicted to be higher than alternatives for phthalates and Bisphenol A and similar for parabens.

4. For nanomaterials its difficult to predict from amount and exposure route, need to expand databases, need to know dosimetry to interpret results from in vivo and in vitro studies.

Thank you

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Extra Slides

Alternative Chemicals

- **Phthalates:** Example alternatives to phthalates included in this paper are Aceyl tributyl citrate, Di-isononyl-cyclohexane-1, 2 dicarboxylate, dioctyl terephthalate, epoxidized soybean oil, alkylsubphonic phenyl ester, tri-2-ethylhexyl trimellitate, acetylated monoglycerides of fully hydrogenated caster oil, bis (2-ethylhexyl), 4-benzenedicarboxylate, di (2- ethyl hexyl adipate), di-butyl adipate, butylated hydroxytolulene, hyper branched poly, di (2 ethylhexyl) phosphate, tri (2ethylhexyl) phosphate, o-tolulene sulfonamide, 2,2,4 trimethyl 1,3 pentanediol diisobutyrate, diocytl sebate and dibutyl sebate [15].

- **BPA:** The primary alternative expoxy resins for BPA are BPS and BPF [9].

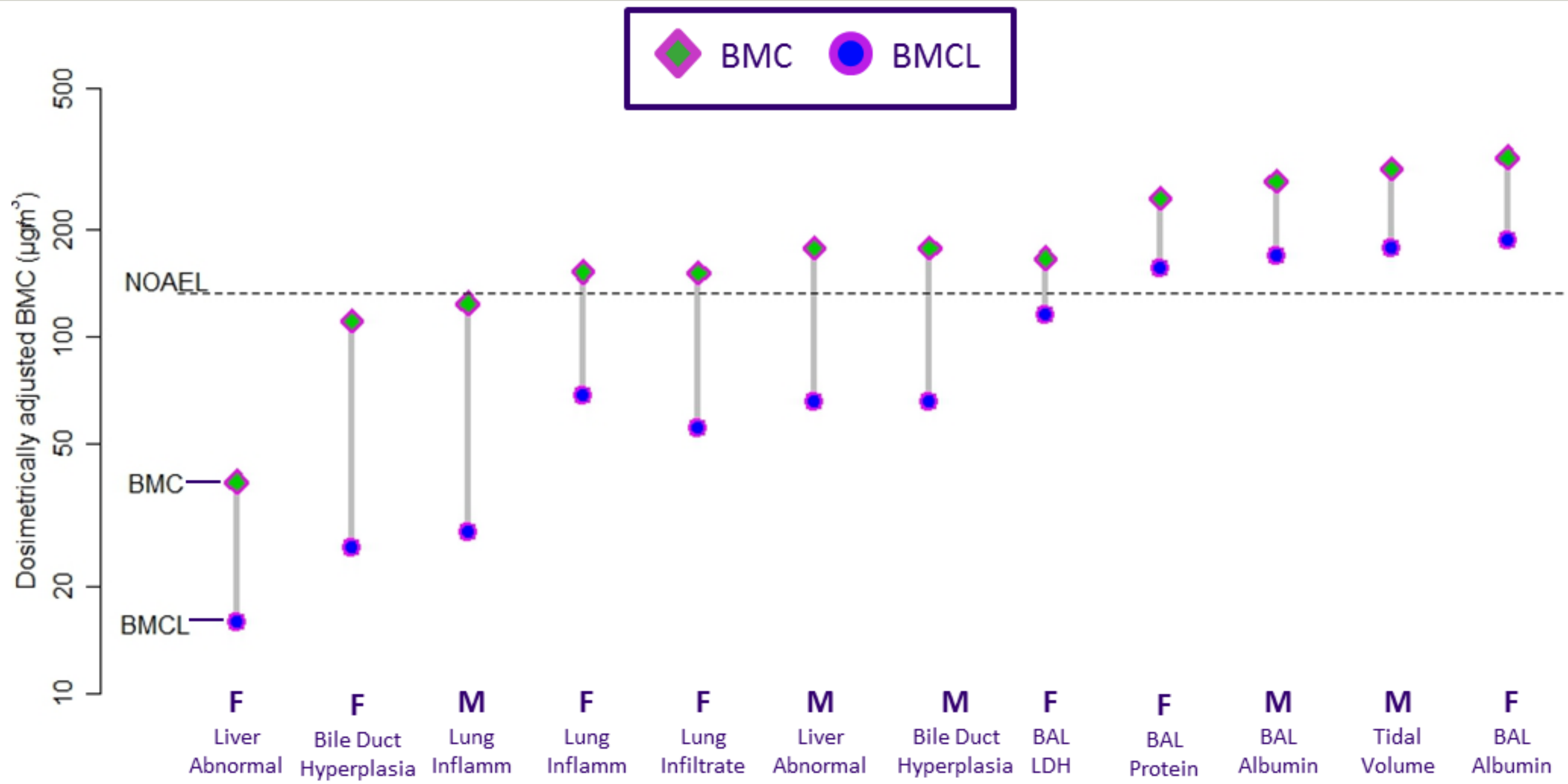
- **Parabens:** Identification for alternative preservatives for parabens include Benzoic acid, Potassium sorbate, Sodium benzoate, Sorbic acid [18]

Numeric Coverage of Alternatives

Table 1: Number of chemicals within each chemical group included in authoritative lists and reports, animal in vivo databases and in vitro databases for conventional and alternative chemicals

Conventional Chemicals			
Chemical Group	Authoritative Lists and Report Coverage	Animal in vivo Coverage	In vitro Coverage
Bisphenols	1 out of 1	1 out of 1	1 out of 1
Parabens	2 out of 4	3 out of 4	4 out of 4
Phthalates	8 out of 9	7 out of 9	6 out of 9
Alternative Chemicals			
Bisphenols	0 out of 3	2 out of 3	3 out of 3
Parabens	0 out of 4	4 out of 4	3 out of 4
Phthalates	1 out of 17	10 out of 17	14 out of 17

Dosimetrically adjusted BMC and BMCL comparison



Histopathological, functional, and bronchoalveolar lavage endpoints

Weldon et al. 2016

Moving into the Future:

- Existing regulations of children's consumer products apply to well characterized chemicals
  - Lead, cadmium, phthalates, BPA
- Lists for required reporting include chemicals known to be toxic to children
  - For example: Methyl ethyl ketone, formaldehyde
- Updating these regulations can be time consuming
- How do we evolve as new hazards come on the market? Examples for nanomaterial illustrate this challenge