NTP
National Toxicology Program

Screening for Biological Activities of Concern in Children's Products

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NTP Board of Scientific Counselors Meeting
June 29, 2017

Topics

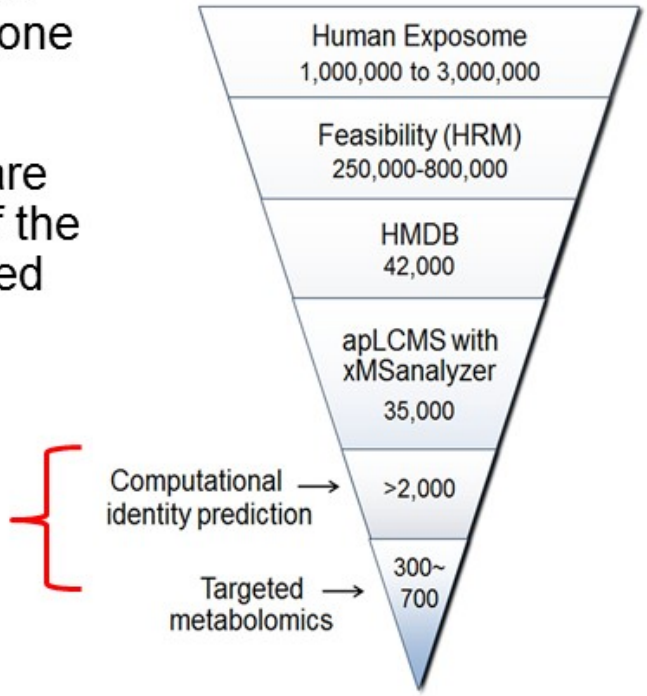
- Rationale, request
- Utility, applicability
- Feasibility, examples
- Approach, challenges

One at a time

We can detect far more chemicals than we can identify

- "…there appears to be no choice but to abandon the limitations of measuring one chemical at a time."
- "…most chemicals to which humans are exposed, the so-called "dark matter of the exposome", are largely uncharacterized and have minimal or no evaluation concerning toxicity."

Chemicals of concern that might be measured or reported or limited in a product are in this range



Uppal et al. *Chem. Res. Toxicol.*, **2016**, *29*, 1956

Home is where the exposures are

Consumer Product Chemicals in Indoor Dust: A Quantitative Meta-analysis of U.S. Studies

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Environ. Sci. Technol., **2016**, *50* (19), pp 10661–10672
DOI: 10.1021/acs.est.6b02023
Publication Date (Web): September 14, 2016

Children's products safety concerns

Consumer Product Safety Commission wants lead out of kids products

Consumer Product Safety Commission seeks to ban the toxic metal from children's products after Mattel's 2nd recall of Chinese imports - critics say it should have been done years ago

Jane Kay, Chronicle Environment Writer Published 4:00 am, Wednesday, August 15, 2007

BREAST CANCER FUND
Prevention Starts Here
Campaign for Safe Cosmetics

October 2016

Pretty Scary 2

Unmasking toxic chemicals in kids' makeup

All I want for Christmas is a toxic-free Disney

Connecticut Department of Health

- "Consider applying Tox21 techniques to consumer products designed for use by young children"
- Basis of concern
- What research did they request NTP carry out?
- How might the information be used?
- Who else has a similar need?

Request

- Rationale
  - Uncertain whether existing chemical of concern (CoC) lists reflect the composition of products currently on the market
  - Other biologically active chemicals currently in products that have yet to 'emerge'
- Suggested approach
  - Testing of a product class by compositing across multiple brands
  - Determine the range of activity within product classes
  - Analysis to identify the chemical(s) producing the bioactivity
- Utility
  - Not for risk assessment or other quantitative analysis initially
  - Identify priority products for alternatives analysis

Types of childrens products

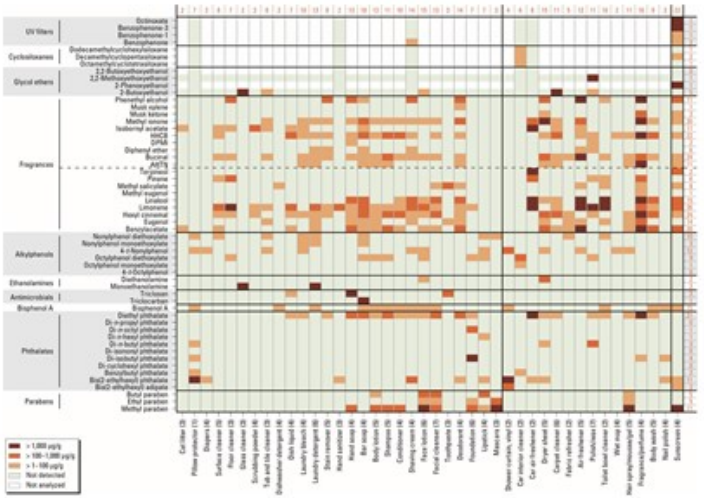
- Infant sleepwear
- Crib and car seat padding
- Sleep mats
- Diapers
- Teethers and pacifiers

1-24 of 4,340 results for **Baby Products** : **Feeding** : **Pacifiers & Accessories** : **Pacifiers**

- Plush toys
- Bath toys
- Toy jewelry
- Plastic clothing items
- Baby bottles

Chemicals in consumer products

- Plasticizers
- Stabilizers
- Antioxidants
- Flame retardants
- Solvents
- Surfactants
- Plastic monomers
- Inks and pigments
- Preservatives
- Adhesives



Dodson et al Environ Health Perspect 2012

Chemical and Product Categories (CPCat)

What is CPCat?

CPCat (Chemical and Product Categories) is a database containing information mapping more than 43,000 chemicals to a set of terms categorizing their usage or function. We have compiled a comprehensive list of chemicals with associated categories of chemical and product use by compiling publically available sources. Sources include, but are not limited to: the Substances in Preparation in Nordic Countries (SPIN) database, information provided by companies, trade associations, and regulatory agencies such as the U.S. Environmental Protection Agency (EPA) and Food and Drug Administration (FDA), the DrugBank database of pharmaceutical products, and information mined from the Aggregated Computational Toxicology Resource (ACToR) database developed by the U.S. EPA. Unique use category taxonomies from each source are mapped onto a single common set of ~800 terms.

The user can search for chemicals by chemical name, Chemical Abstracts Registry Number (CASRN), or by CPCat terms (i.e. category names) associated with chemicals.

Web Application

CPCat Dashboard

Chemicals of Concern

- Heavy metals
- Organotins
- Bisphenol A
- Phthalates
- Alkylphenol ethoxylates
- Perfluoroalkyls
- Parabens
- Triclosan
- Benzophenones
- Formaldehyde releasers
- Siloxanes
- VOCs

Children's Safe Product Act

Hazardous Waste & Toxics Reduction > Children's Safe Product Act > Chemicals of High Concern to Children

The Reporting List of Chemicals of High Concern to Children (CHCC)

Note: The authoritative version of the Reporting List of Chemicals of High Concern to Children (CHCC) is found in WAC 173-334-130.

Each of the chemicals on this list meets the criteria established by the Children's Safe Product Act (RCW 70.240.030). Click on the CAS number for a chemical to view a summary of toxicity and exposure information for that chemical, prepared by the Washington State Department of Health. (Read background information on these summaries here.)

Addressing Chemicals of Concern

ECHA works together with the European Commission and the EU Member States for the safety of human health and the environment by identifying the needs for regulatory risk management at an EU-wide level. The Member States or ECHA (at the request of the Commission) initiate the identification of substances of very high concern and restrictions, and Industry can submit applications for authorisation. The process for harmonised classification and labelling of substances may be initiated by Member States and by manufacturers, importers or downstream users.

ECHA welcomes all members of the public to give their contributions during the different consultation phases of the authorisation, restriction and harmonised classification and labelling processes. Under the Biocidal Products Regulation, stakeholders can provide information on potential candidates for substitution.

Mind Store

The Hazardous 100+ List of Chemicals of High Concern

Safer Chemicals Healthy Families

Hazardous 100 List (Last updated: 7/17/13)			Authoritative Lists (see key below)*						www.saferchemicals.org		
Chemical Name	CASRN	Chemical Acronym or Synonym	CALIFORNIA	MAINE	MINNESOTA	WASHINGTON	US EPA	EU REACH	Primary Type of Toxicity	Reference for Toxicity Information (see key below)	Primary Category
2-Aminotoluene	95-53-4	o-Toluidine	x	x		x		C	cancer	1	Dyes & Pigments
2-Naphthylamine	91-59-8		x	x					cancer	1	Dyes & Pigments
3,3'-Dimethylbenzidine*	119-93-7	o-Tolidine	x			x	x		cancer	1	Dyes & Pigments
4,4'-Bis(dimethylamino)benzophenone	90-94-8	Michler's ketone	x					C	cancer	1	Dyes & Pigments
4,4'-Methylenedi-o-toluidine	838-88-0		x					C	cancer	1	Dyes & Pigments

Regulatory drivers (impact)

State Legislation

- Washington Children's Safe Products Act (CSPA)
- Maine Toxic Chemicals in Children's Products
- California Safer Consumer Products (SCP) Program

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COMMISSIONER

APPENDIX V

Chemicals of High Concern

Maine Department of Environmental Protection
Process Documentation for
Investigating Chemical Presence in Consumer Products

June 29, 2012

International Journal of
Environmental Research and Public Health

MDPI

Article

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

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SAFER
CONSUMER
PRODUCTS

Priority Product
Work Plan

Three Year Work Plan | 2015 - 2017

APRIL 2015

SAFER CONSUMER PRODUCTS BRANCH

DEPARTMENT OF TOXIC SUBSTANCES CONTROL

Substances in Articles

- "Article 33 of the REACH Regulation…for the supplier of a product one or more constituent articles of which contain(s) a Candidate List substance of very high concern in a concentration above 0.1% weight by weight of that article, to inform the recipient and, on request, the consumer, of the presence of that substance by providing them, as a minimum, with the name of the substance in question."

DECIDING WHAT IS AN ARTICLE UNDER REACH

Goals

- Identify critical questions to address, possible approaches that align with NTP capabilities and provide foundation for further progress
- Use NTP expertise and capabilities, leveraged with others who have interest, to provide information to CT DPH and other stakeholders
- Identify artifacts, pitfalls, issues that confound interpretation and limit utility for decision-making

Decisions

- Should NTP do it?
- Why NTP?
- Why would we not?
- What could we do?
- What are the challenges and risks?
- For how long?
- Why would we stop?
- What is success?

Key Issues

- Significant uncertainty regarding relationship between level in a product and migration or human exposure/dose, relative importance of different sources to internal dose
  - Bioactivity screening in some form has been utilized in product development for decades
  - Availability and advancement of technology for non-targeted analysis
- If a chemical of concern can migrate out and lead to dose, then presume other components of unknown toxicity may also result in internal dose
- Suitability of current assays, technologies, workflows being employed e.g. in Tox21

Approach

- Develop a few pilot projects designed to answer critical questions that will stimulate further innovation in the field
- Are there accepted methods for identifying and sampling representative commercial products that are suitable for pilot scale investigations? For generating composite samples?
- Are there available/acceptable methods for creating extracts that reflect bioaccessibility under normal human use conditions?
- Non-targeted analysis to compare among product extracts with different bioactivity may identify specific chemicals or chemical-effect associations to follow up on

A few examples

- Early days: *Limulus*
- CALUX
- Escher et al. *Env Sci Technol* 2014
- Kadimisetty et al. *ACS Sensors* 2017
- Extractables and leachables in drug packaging and medical devices
  - FDA, ISO, USP, ASTM guidance, standards, methods

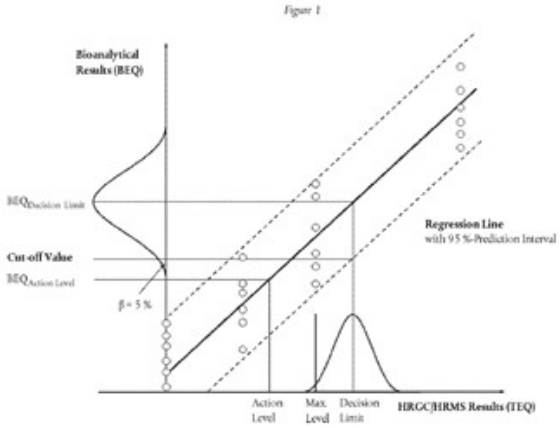
Examples of bioactivity based screening

CALUX

- *Screening method* for monitoring for the presence of PCDD/Fs and dioxin-like PCBs in feed – Bioanalytical equivalents (BEQ)

  Commission Regulation (EU) No 709/2014 of 20 June 2014 amending Regulation (EC) No 152/2009 as regards the determination of the levels of dioxins and polychlorinated biphenyls OJ L 188, 27.6.2014

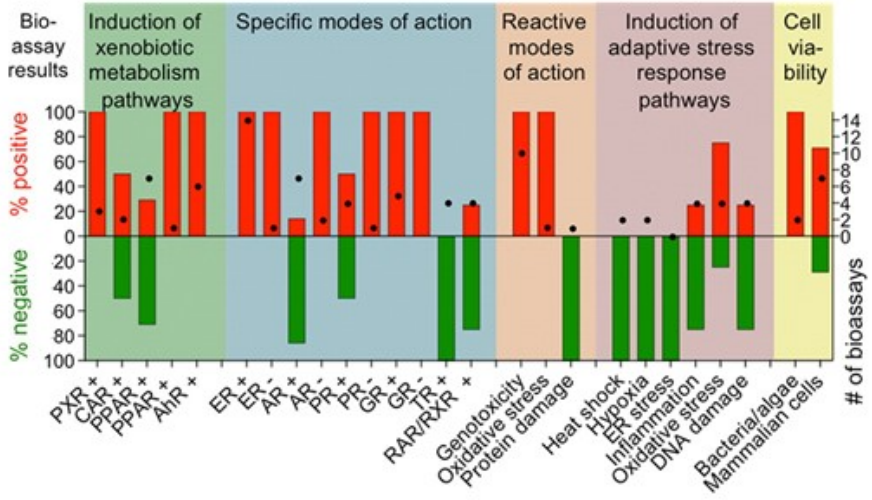
- Zhao et al. (2013) Common Commercial and Consumer Products Contain Activators of the Aryl Hydrocarbon (Dioxin) Receptor. PLoS ONE 8(2): e56860
  - "…identity of the responsible AhR-active chemicals and their toxicological impact remain to be determined"



Examples of bioactivity based screening

Escher et al *Env Sci Technol* 2014

- 20 laboratories, 103 unique in vitro bioassays, 10 water samples
- 65 bioassays (63%) positive in at least one sample
- Characteristic bioanalytical profiles
- Xenobiotic metabolism (PXR, AHR), hormone-mediated (ER, GR, anti-AR), reactive (genotoxicity) and adaptive stress response (oxidative stress)



A project would not address…

- A comprehensive analysis of CoCs in consumer products - will not look at all CoCs or all types of products or even necessarily all types of bioactivity of interest
  - Many private and public sector organizations (States, NGOs, EPA) are doing this, requiring this, or compiling data generated by others
- Develop new methods for determining extractables and leachables that reflect conditions of use and human exposure
  - Leverage capabilities of agency partners, existing methods used by industry, regulatory, standards organizations
- Attempt to 'chase down' all bioactivities and identify specific chemicals driving responses
  - Potentially limited effort in collaboration with partners

Viability and utility of the approach

- Proof of concept
  - Relevance and utility of “Tox21 approach” in whole new arena
- Is it feasible?
  - Are challenges surmountable?
- Is it useful? To whom? For what?
  - Does bioactivity screening have a role in consumer product safety assessment?
- Is it actionable in a public health context?
  - Is a product that does not contain known CoCs safe?

Questions for BSC Input

- Please comment on whether a research program on this topic is appropriately aligned with NTP's mission, capabilities, and partnerships. What additional inputs should NTP seek? What outputs would be of most value to key stakeholders?