Use of Biomonitoring Data under Canada's Chemicals Management Plan

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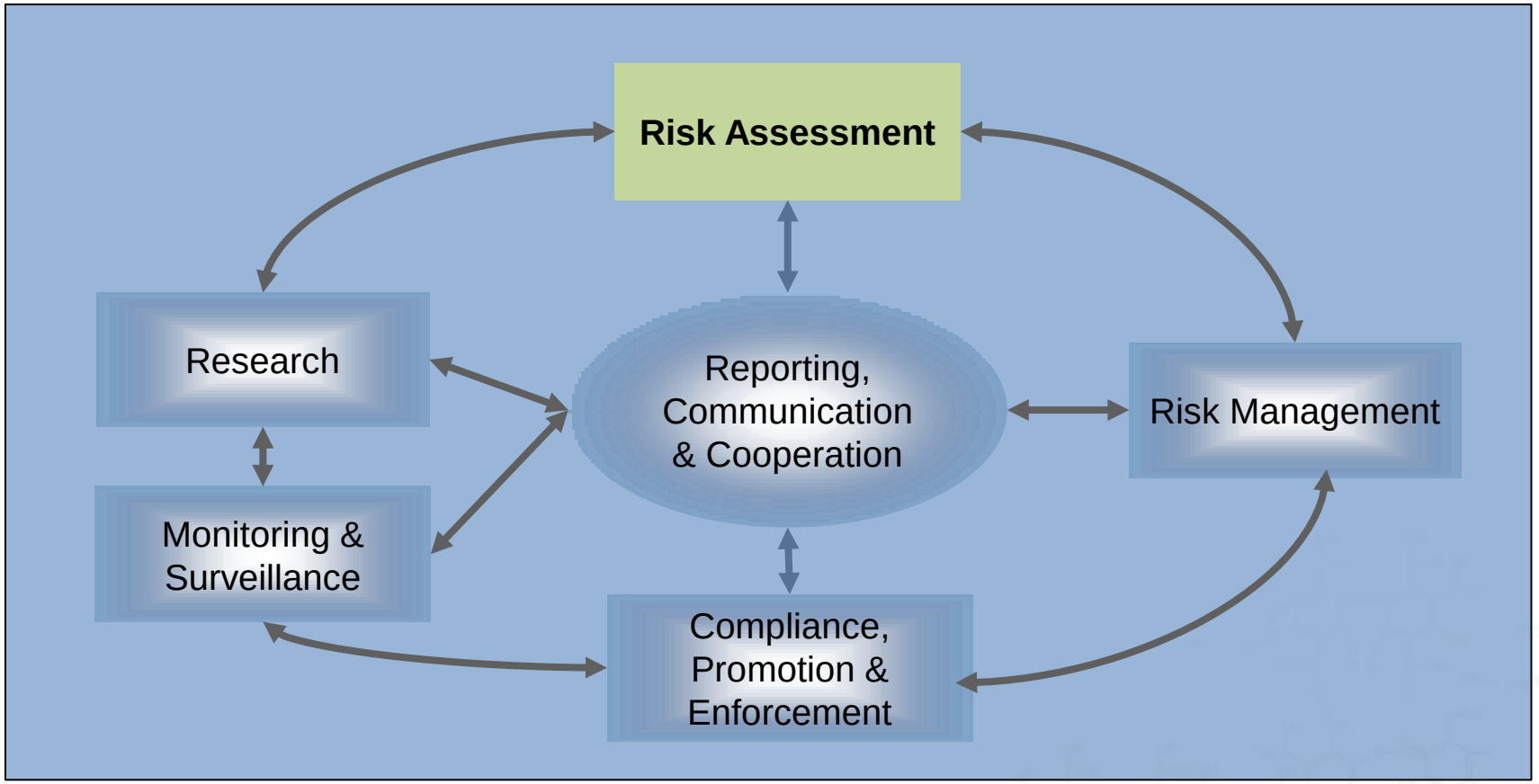
Outline

- Canada's Chemicals Management Plan (CMP)
- Considerations in the Use of Human Biomonitoring (HBM) data in Regulatory Risk Assessment
- How HBM data has been used in CMP Risk Assessments
- Looking forward – Next Phase of CMP

Chemicals Management Plan Cycle and Program Pillars



CMP Risk Assessment Toolbox

Type 1 Approach

- Addresses the substance/group with a science-based policy response
- Used when regulatory assessment conclusion under s.64 of CEPA 1999 is not suitable
- Examples include: Referring to a better placed program (e.g., foods); documentation of previous action under *CEPA 1999*

Type 2 Approach

- Addresses substances using a broad-based approach, often based on low potential for exposure and conservative scenarios
- Substances do not meet criteria under s.64
- Examples include: Rapid Screening; Threshold of Toxicological Concern type approaches

Low

Level of Complexity

High

Type 3 Approach

Type 3-1

- Addresses the substance/group with a reduced amount of effort for streamlined hazard and/or exposure analysis
- Examples include: Use of international hazard characterizations; use of biomonitoring data; qualitative assessment

Type 3-2

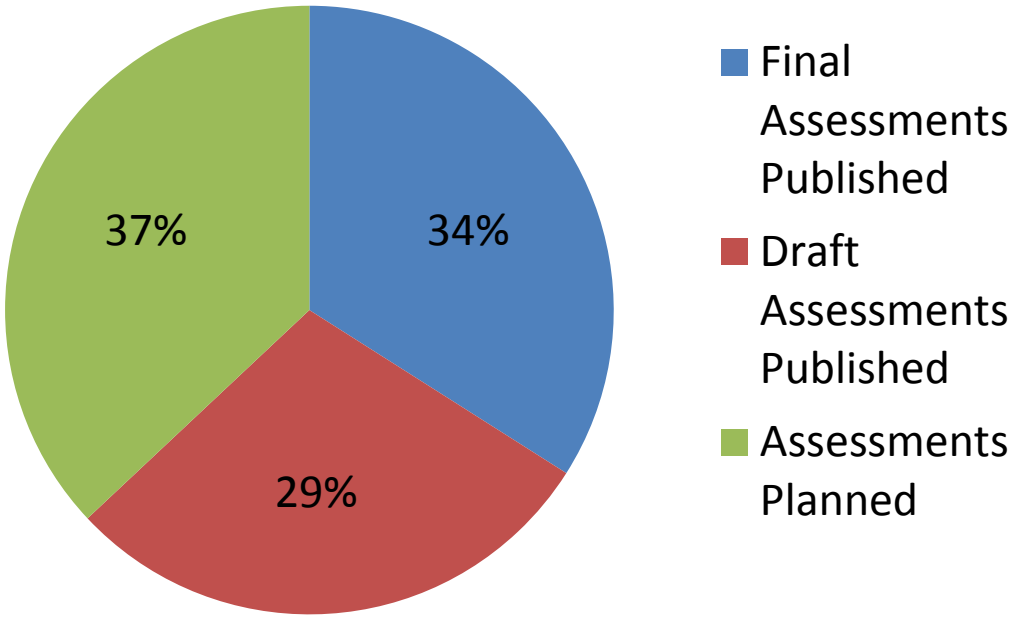
- Substance/group requires de novo risk assessment

Type 3-3

- A complex assessment is required for the substance/group that may require cumulative assessment approaches

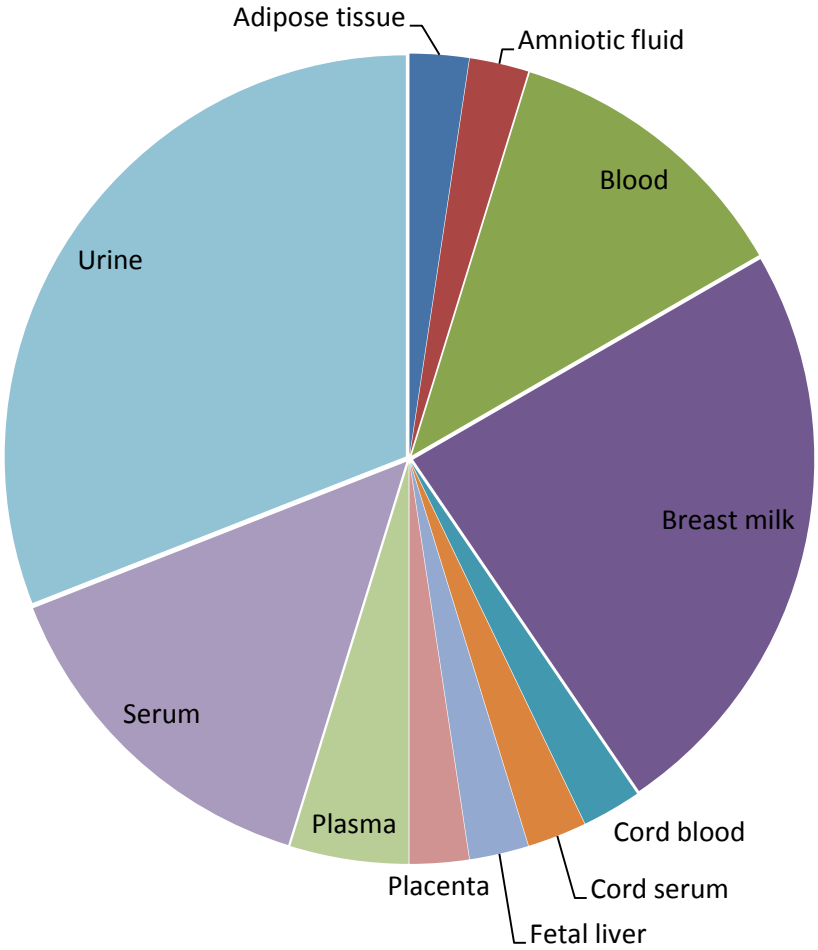
RM actions for those meeting s.64; additional information gathering and source attribution may be required to inform risk management

CMP – Risk Assessment Progress



- Progress to date since the launch of CMP in 2006 on the approximately 4,300 substances identified for further attention
- **~2,740 substances** have been assessed
- ~363 substances or groups of substances have been concluded to be toxic under the *Canadian Environmental Protection Act* (1999).

Availability of HBM Data in CMP



- Of the ~2700 substances assessed to date:
  - ~10% (or ~250 substances) had HBM data
  - ~ 60% of substances with HBM data were 'organic'
  - ~ 75% of HBM data were represented by adult populations only
- For the remaining 1550 substances, an estimated **15-20%** will have HBM data

Considerations for Use of HBM Data in Risk Assessment

- Within the context of Canada's Chemicals Management Plan, there are a number of considerations prior to incorporation of HBM data in human health risk assessment:

  1. Adequacy of the biomarker
  2. Quality of the data
  3. Appropriateness of the Data Set
  4. Approach for interpreting the data

Considerations for Use of HBM Data in Risk Assessment

1. Adequacy of the biomarker
   - ❑ Is the biomarker specific and sensitive
   - ❑ Can it be distinguished from other chemicals?
   - ❑ Are the pharmacokinetics well described?
   - ❑ Can the measured levels be linked to exposure or to critical health effects?
     - Extent of metabolism, toxicokinetic data including half-life

Considerations for Use of HBM Data in Risk Assessment

2. Quality of the data
   - ❑ QA/QC, analytical methods
   - ❑ Type of sample collection & storage
   - ❑ Incomplete or spot urine samples; plasma vs serum vs whole blood; pooled samples
   - ❑ Representativeness
   - ❑ Completeness
   - ❑ Sample size (e.g. use of weighted surveys)
   - ❑ Age of study

Considerations for Use of HBM Data in Risk Assessment

3. Appropriateness of the Data Set

- Geography: is data representative of Canadian population?
  - Considerations for use of foreign data (e.g. likelihood of similar exposures/presence of substance)
- Time Trends: How do levels compare to other data sets/populations
- Sub-populations:
  - Are relevant, vulnerable populations monitored (e.g. children)?
  - What age groups are represented?
  - Can we account for potential gender differences?
  - Occupational vs general population
- Timing: Availability of data for incorporation into risk assessment

Considerations for Use of HBM Data in Risk Assessment

4. Approach for Interpreting the Data

- ❑ Reverse Dosimetry
  - Conversion of exposure concentration(s) in a biological matrix to external dose(s) (mg/kg/day)
- ❑ Forward Dosimetry
  - Conversion of an external exposure associated with a critical health effect to an internal dose
- ❑ Direct Comparison
  - If the biomarker concentration (blood or urine) associated with a critical health effect is known, biomarker concentrations in humans (from a HBM study) can be directly compared

Use of HBM Data in CMP Risk Assessments

Use of HBM Data has evolved from qualitative to quantitative use including:

- Examining exposure trends and patterns:
  - By sex, (e.g. triclosan) ,age (e.g. PFOA), geography or subpopulations (e.g. selenium), or overall exposure patterns (e.g. cobalt)
- Examining potential association/correlation with health outcomes from cross-sectional health surveys, prospective or retrospective epidemiology studies
  - E.g. Lead (neurodevelopmental); selenium (T2 diabetes)
- Estimating external intakes of exposure
  - Dose-reconstruction or reverse dosimetry (e.g. triclosan, phthalates)
- Comparing with health effects data (exposure guidance values)
  - Directly → lead
  - Indirectly (Forward dosimetry) → selenium; cobalt

Use of HBM Data in Risk Assessment

- Several CMP assessments have used HBM data quantitatively to make conclusions about the potential for risk to human health:
  - PBDEs, HBCD, BPA (use of breastmilk data for estimating dietary intakes of infants)
  - PFOA and PFOS (comparison of blood levels in Canadians with serum levels in rodents from toxicity studies)
  - Lead (whole blood – comparison with neurodevelopmental effects)
  - Cobalt (use of existing biokinetic model studies to derive blood equivalent concentrations to the critical health effect)
  - **Triclosan (spot urine)**
  - **Selenium (whole blood)**
  - **Phthalates (spot urine)**

Case Study #1 - Triclosan

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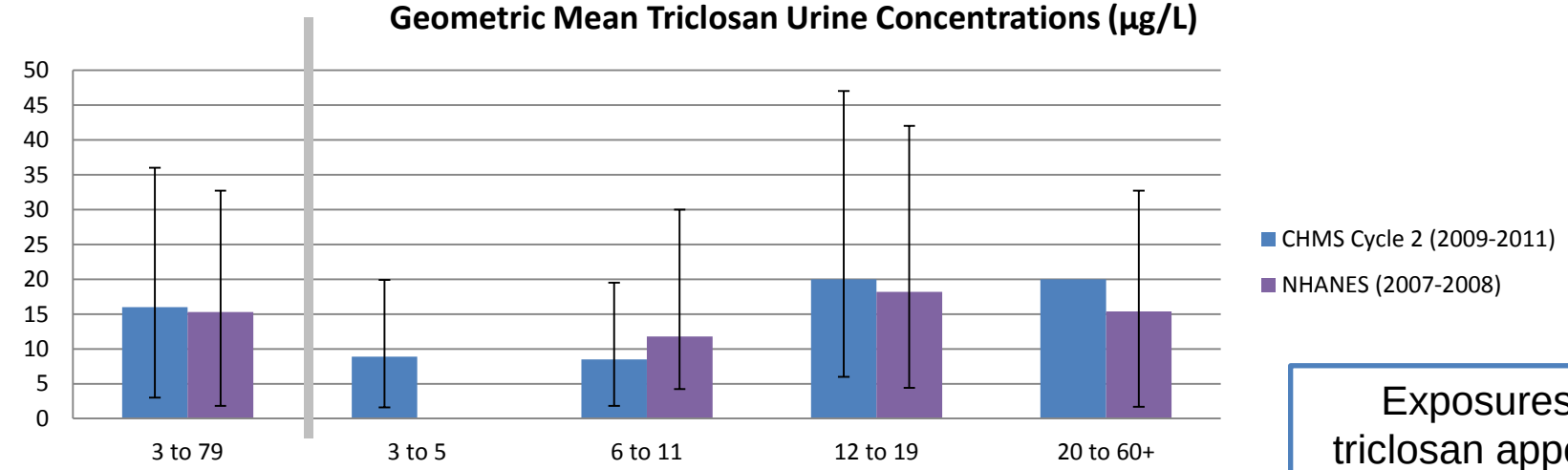
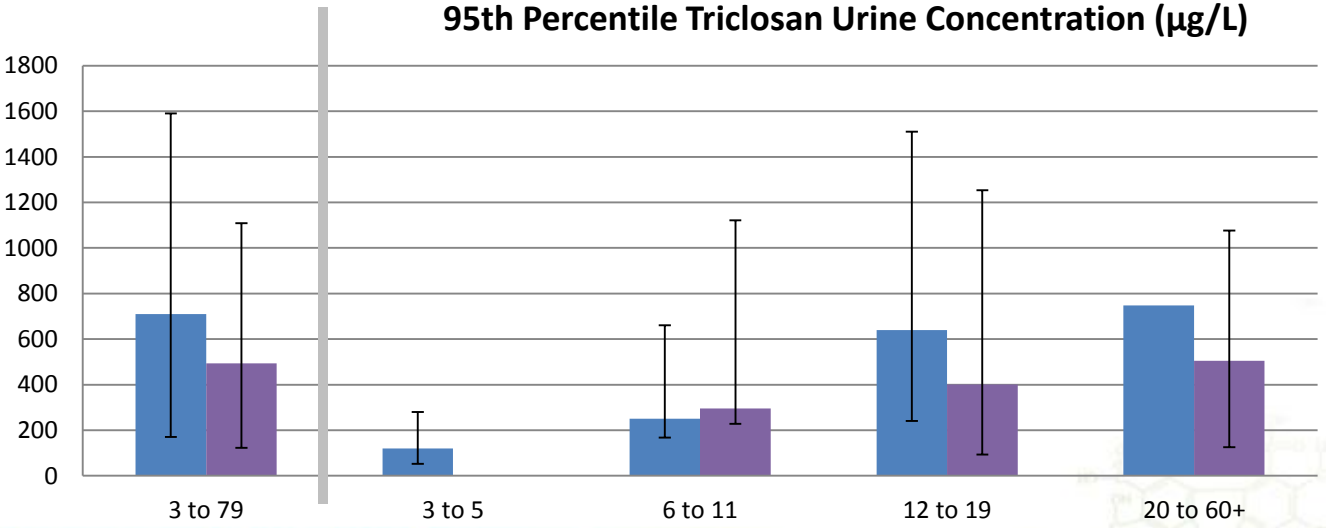
- Draft 2012 assessment used intake estimates derived by the US EPA (OPP)
  - Similar availability of consumer products (personal care products, drugs) and use
- Intake estimates in mg/kg/day estimated from spot urine concentrations
  - Reverse-dosimetry from NHANES data; Mass balance approach
  - Key inputs: biomarker concentration, 24hr urine volume, body weight and the fraction urine excretion
  - Dose-reconstruction of average and upper-bounding urine concentrations
- Exposure and patterns of exposure
  - Similar exposures in Canada & US; patterns by age (adolescent exposures higher than adults, infants and children)
- Draft assessment identified no health risk (final to be released 2016)

Geometric Mean Triclosan Urine Concentrations (µg/L)



95th Percentile Triclosan Urine Concentration (µg/L)

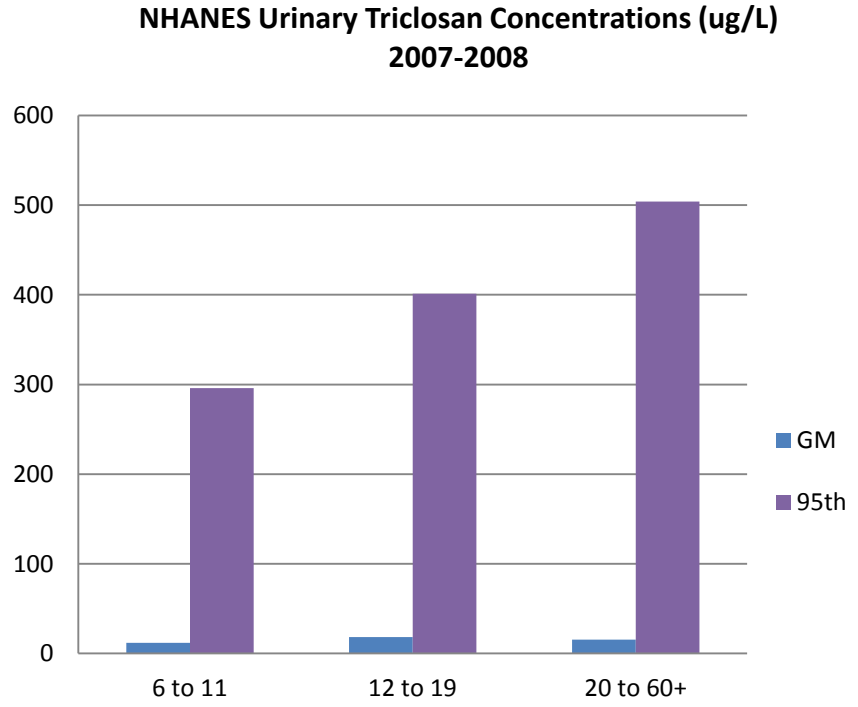


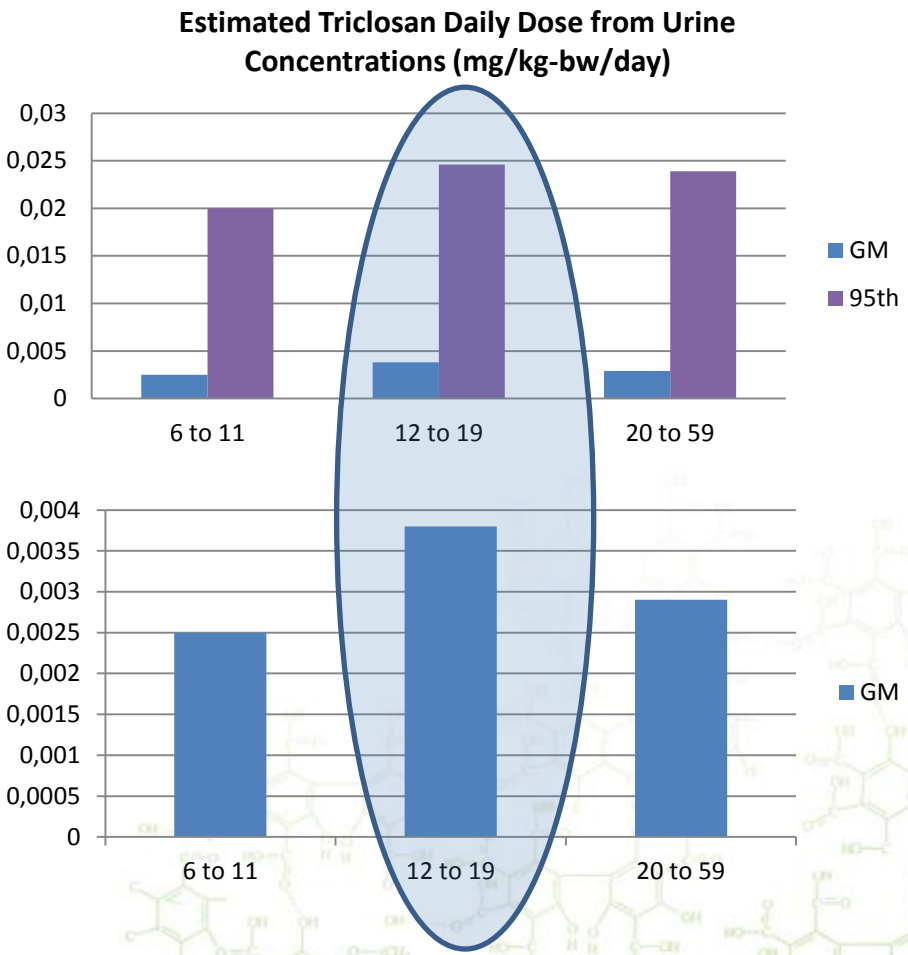
Exposures to triclosan appear to be similar in Canada and USA (slightly higher in Canada)

Error bars represent 95% Confidence Intervals

Case Study – Triclosan

Highest urine concentrations does not necessarily mean highest estimated dose/intake





Sources of Triclosan HBM Data by Population

Unique exposures such as nursing, mouthing

U.S NHANES

6 to >79 years old

Fetus | Infants (< 1 month) | Infants (2-3 months) | 2 to 3 years old | 3 to 5 years old | 6 - 11 years old | 12 - 19 years old | 20 - 59 years old | 60 - 79 years old

P4 Study
Fetus (meconium)
Infants (< 1 month)
Infants (2-3 months)
Breastmilk

Pregnant Women

MIREC CD Plus
Children (1-3)

CHMS
Children (3-11)
Adolescents (12-19)
Adults (20-79)

Pregnant women

MIREC
Pregnant Women

Case Study #2 - Selenium

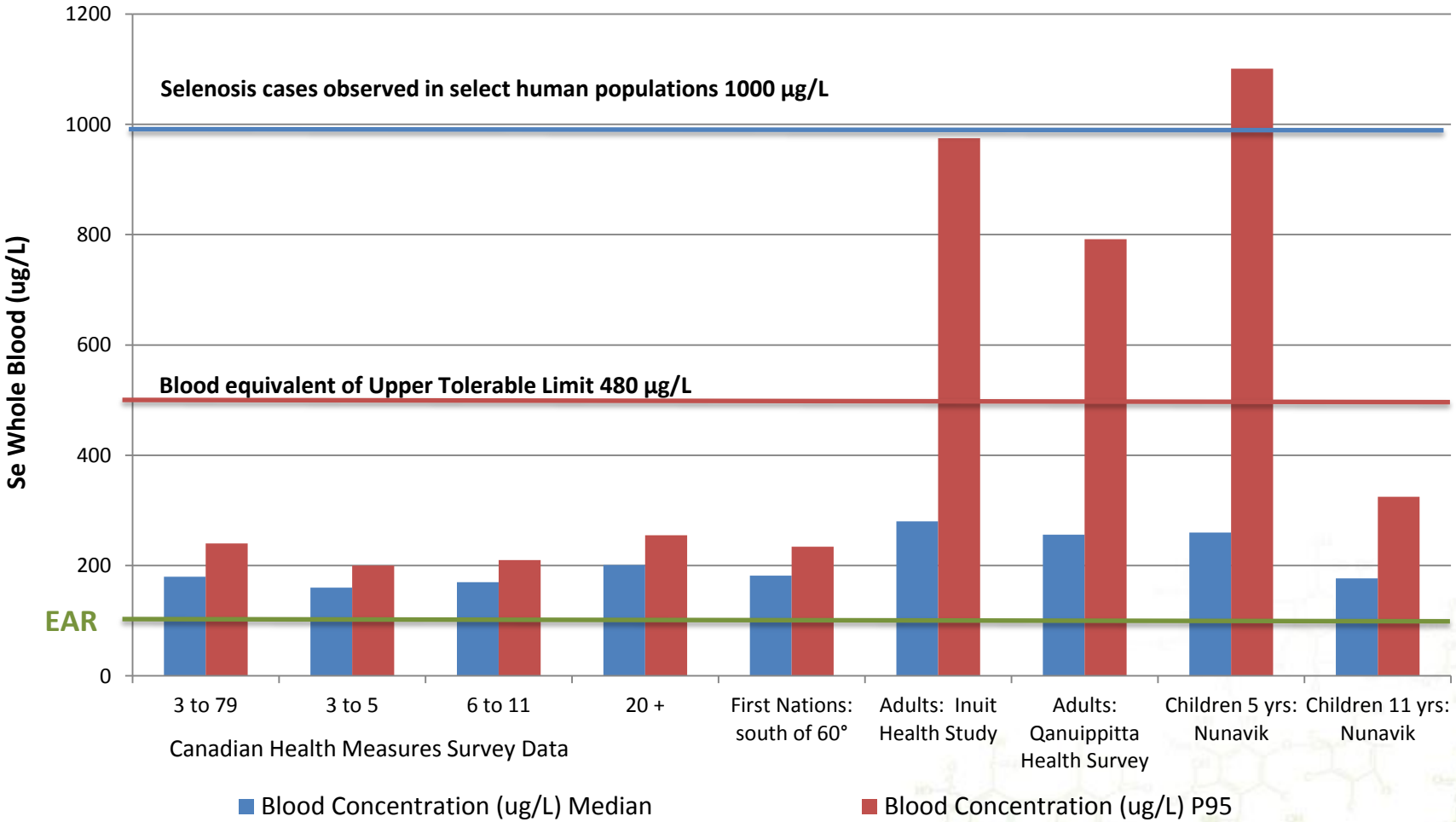
Case Study #2 - Selenium

- Selenium present in food, drinking water, air, soil, dust; other sources of exposure include cosmetics, mineral supplements, drugs, consumer products
- Measured in a wide variety of biological media
- Compared with health effect endpoints using forward dosimetry (along with traditional intake estimates for environmental media)
  - Based on a comparison of whole-blood concentrations to a whole-blood equivalent
  - Required to convert the critical health effect dose (ug/day) to a biomarker equivalent concentration (µg/L) to compare with HBM data
- Pharmacokinetic data and epidemiological studies used to derive a quantitative relationship between blood concentrations and intake

Case Study #2 - Selenium

- Quantitative relationship used to convert Institute of Medicine (IOM) Tolerable Upper Intake Level (UL) into a blood equivalent
  - Based on data from epidemiological studies where data on blood concentrations association with intake estimates and health effects (selenosis) were available
- UL of 400 µg/day established by the IOM based on a NOAEL of 800 µg/d for selenosis observed in a Chinese cohort by Yang and Zhou (1994), adjusted by an uncertainty factor (UF) of 2
- The resulting whole-blood equivalent for the reference dose was calculated to be 480 µg/L (Hays et al. 2014)

Case Study #2- Selenium



EAR: Estimated Average Requirement = 100 ug/L

Selenium – What did we learn?

- Essentiality can be taken into account in assessments that use HBM data
  - Evaluated population level exposure against nutritional values
- Trends and changes in exposure and patterns of exposure
  - Patterns by age (children have significantly lower [Se blood] than adults)
  - Differences observed by region/geography (e.g. northern Canada)
  - Subpopulations (e.g. selenium higher in Inuit)
- Draft assessment identified potential concerns in Inuit populations otherwise difficult to detect without HBM in these subpopulations.
- HBM likely unable to capture use of uncommon multi-vitamin products or subsistence fishers near point sources of selenium (e.g. mining operations)

Case Study #3 - Phthalates

Case Study #3 - Phthalates

- Intake estimates estimated from spot urine concentrations with creatinine adjustment
- Dose-reconstruction of entire distribution:
  - Individual data used, due to metabolism – multiple metabolites in urine summed at the individual level.
  - Central tendency and upper bounding (P95) used in risk characterization (along traditional intake estimates)
  - Based on human PK data, with some read across based on similar metabolism profiles (as supported in literature - CHAP, Kransler et al 2012, Wittasek et al 2007, Koch and Calafat 2009)
- Differences in metabolism between short-chain and LMW medium chain phthalates and HMW medium chain phthalates/long chain phthalates
- HBM data in select phthalates provided support for cumulative risk assessment (to be published 2016)

Phthalates - Potential Sources of Exposure

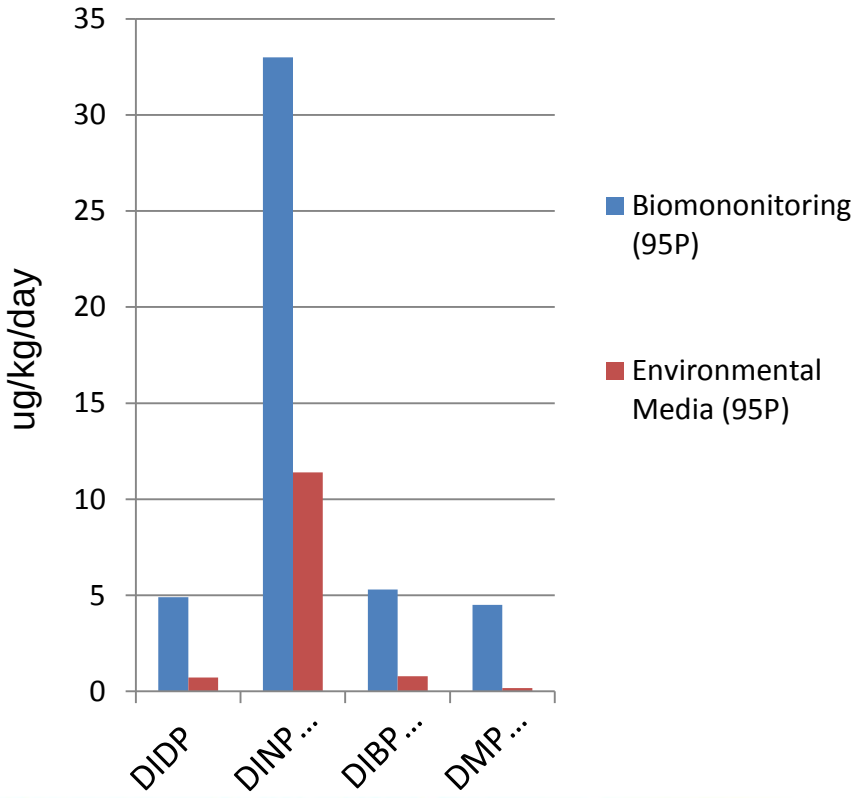
Short Chain

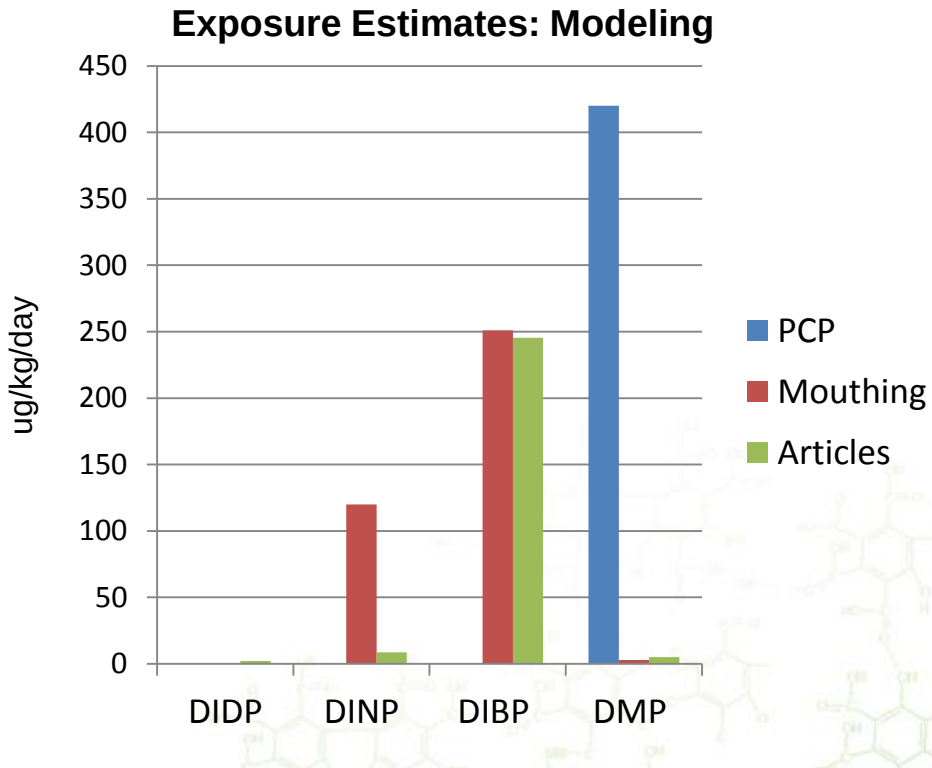
Medium Chain

Substance	Environmental Media and Food	Consumer Products	Biomonitoring Intakes
DMP	Breast Milk , Food Dust , Indoor Air	Cosmetics , TBD	Yes
DIBP	**Breast Milk, Food, Dust, Indoor Air**	**Children's toys and articles, PVC articles, DIY Products, cosmetics**	**Yes**
BCHP	**N/A**	**N/A**	**N/A**
CHIBP	**N/A**	**N/A**	**N/A**
DCHP	**Dust**	**DIY Products**	**Not Quantified (absence of PK data)**
DBzP	**Dust**	**N/A**	**N/A**
DMCHP	**Dust**	**N/A**	**N/A**
DIHepP	**Dust**	**DIY Products**	**N/A**
B79P	**Dust**	**DIY Products, PVC Articles**	**N/A**
BIOP	**N/A**	**N/A**	**N/A**
B84P	**Dust**	**DIY Products, PVC Articles**	**N/A**
DINP	**Food, Dust**	**Children's toys and articles, PVC articles, DIY Products**	**Yes**
DIDP	Food , Dust	TBD	Yes
DUP	TBD	TBD	N/A

Case Study #3 - Phthalates

Comparison of Exposure Estimates based on HBM with others Sources of Exposure





DIDP – highest exposures 20 years plus
DINP – highest exposures 12-19 year olds
DIBP, DMP– highest exposures 6 to 11 years olds

HBM Data - Limitations of Use in HHRA

- Not all chemicals are monitored (e.g., issues with sampling techniques)
- The presence of a chemical does not necessarily mean an adverse health effect will occur
- Absence of a chemical does not mean that an exposure did not occur
- HBM data alone cannot determine the source or route of exposure
- Relevance & translation of occupational exposure to other populations
- Knowledge of chemical-specific pharmacokinetics and the characteristics of the biomarker as a measure or representative of the external exposure of interest

Uncertainties → HBM Data in Risk Assessment

- Hazard data typically based on intake levels (mg/kg/day) vs. internal exposure. For quantitative use in risk characterization, these levels need to be linked.
- There is uncertainty associated with the assumption of steady-state
- Assumptions made to convert spot urine to amount excreted over 24 hr
  - Spot urine data may require correction based on assumptions (e.g. urine volume creatinine excretion, specific gravity)
  - Often assume fractional urinary excretion is constant across age groups and irrespective of route of exposure
  - If assumptions are based on adult factors (e.g., urinary flow, excretion factor) may not be appropriate to use in conjunction with infant or toddler HBM data

Looking Forward in CMP

- HBM data exists for many substances which require assessment under CEPA:
  - Inorganics: Ag, Ba, Be, B, Cu, CN, I, Mn, Mo, Sn, Tl, V, Zn
  - Organics: flame retardants, triclocarban, parabens, musks
- Currently examining:
  - Use of Biomonitoring Equivalents or HBM values
  - Tiered approach or fit for purpose assessment
  - May not be necessary to increase the complexity of risk assessments when adequate HBM data is used

Acknowledgements

- Kristin Macey
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- Mikin Patel
- Sandra Kuchta

For more information

- **PFOS/PFOA**: http://www.ec.gc.ca/ese-ees/370AB133-3972-454F-A03A-F18890B58277/PFOA_EN.pdf
- **Triclosan:** http://www.ec.gc.ca/ese-ees/6EF68BEC-5620-4435-8729-9B91C57A9FD2/Triclosan_EN.pdf
- **Selenium**: http://www.ec.gc.ca/ese-ees/301B5115-F8B7-430D-8EFA-290903B5FAD1/DSAR_Grouping_Selenium_EN.pdf
- **Cobalt:** http://www.ec.gc.ca/ese-ees/4A8C8BC4-3854-4126-97EE-4C167D895DDE/DSAR_Grouping-Cobalt_EN.pdf
- **Lead:** http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/dhhssrl-rpecscepsh/index-eng.php
- **Phthalates**: http://www.chemicalsubstanceschimiques.gc.ca/group/phthalate/index-eng.php

References

- Hays SM, Macey K, Nong A, Alyward L. 2014. Biomonitoring equivalents for selenium. Reg Pharm Tox 70(1):333-339.
- Yang G, Zhou R. 1994. Further observations on the human maximum safe dietary selenium intake in a seleniferous area of China. J Trace Elem Elect H 8:159-165.
- United States Consumer Product Safety Commission Chronic Hazard Advisory Panel. 2014. Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives Final Report. Available from: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf
- Kransler KM, Bachman AN McKee RH. 2012. A comprehensive review of intake estimates of di-isononyl phthalate (DINP) based on indirect exposure models and urinary biomonitoring data. Regul Toxicol Pharm 62:248-256.
- Wittasek, M and Angerer J. 2007. Phthalates: metabolism and exposure. International Journal of Andrology. 31: 131-138.
- Wittassek M, Koch H, Angerer J, Bruning T. 2011. Assessing exposure to phthalates the human biomonitoring approach. Mol. Nutr. Food Res. 55:7-31.
- Koch HM, Calafat AM. 2009. Human body burdens of chemicals used in plastic manufacture. Phil.Trans.R.Soc.B 364:2063-2078

Appendix

Case Study 1 - Triclosan

$$D = \frac{[Urine_{Conc} * Urine\ Volume]}{[FUE]}$$

Where:

- D = Estimated daily dose (µg/kg-bw per day)
- $Urine_{Conc}$= Concentration of triclosan in urine, unadjusted (µg/L)
- $Urine\ Volume$= Average and 95th percentile daily urine volume (L/kg-bw per day) from (Geigy, 1981)
- FUE= Urinary excretion fraction for triclosan

Case Study 2 - Selenium

$$\log BSe = 0.767 \times \log DDSe - 2.248,\ r = 0.962$$

Where BSe is total selenium in whole blood in mg/L, DDSe is daily intake of selenium in µg/day

Case Study 3: Reverse Dosimetry – Phthalates

Creatinine adjustment :

- $Daily\ intake(\mu g/kg\ /day) = \frac{C_{SUM}\left(\frac{moles}{g\ Cr}\right) \times CER\left(\frac{g}{day}\right) \times MW_{parent}\left(\frac{g}{mole}\right)}{FUE_{Sum} \times BW\ (Kg)}$

Where:

- $C_{SUM}\left(\frac{moles}{g\ Cr}\right)$ = sum of molar concentrations of the metabolites
- CER = Creatinine excretion rate using Mage equation
- MW = Molecular weight
- FUE_{Sum} = Sum of fractional urinary excretion values of the metabolites
- BW = Body weight of the participant