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Risk Characterization in Health Risk Assessments under CMP

Health Canada – PAHO Workshop

Lima, Peru

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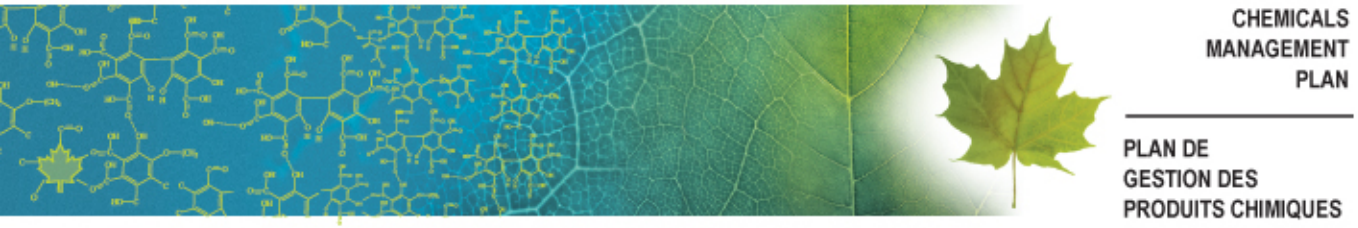

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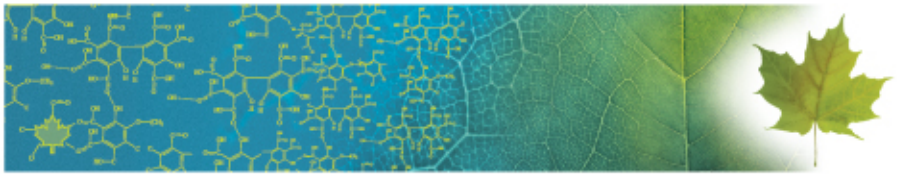
Outline

- Alignment with Risk Assessment Toolbox
  - Type 1 Approach
  - Type 2 Approach
  - Type 3 Approach
- Margins of Exposure
- Human Biomonitoring Data



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

Type 3 Approach

Low

Level of Complexity

High

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

Type 1 Approach

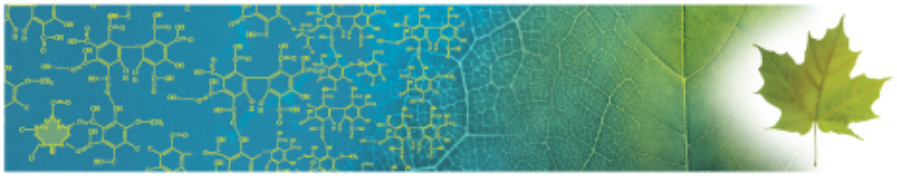
- Qualitative approach to risk characterization
  - Use of a science-based policy decision or when formal conclusion under S.64 not appropriate
    - e.g., substances addressed under Montreal Protocol
    - Previously addressed under CEPA
    - More appropriately addressed under a different Health Canada program
      - Food related substances assess by Health Products and Foods Branch

Type 2 Approach

- Qualitative or semi-quantitative approach to risk characterization
  - Generally adopted for substances for which exposure is anticipated to be very low
  - Substances determined not to be “toxic” under S.64
  - Rapid screening approaches (no direct or indirect exposure sources)
  - Threshold of Toxicological Concern (TTC) approach
    - Screen of health effects data to determine appropriate TTC bin
    - Conservative estimate of exposure compared to TTC bin values
    - If exposure below TTC bin value, substance is considered to be of low concern to health

Type 3 Approaches

- Quantitative
  - Level of refinement/effort minimum necessary to make a decision
  - Rely on existing information to extent reasonable
    - e.g., use of international hazard classifications as critical endpoint and critical effect levels, with update of literature
    - If no acceptable assessment identified, more in-depth de novo assessment required
  - Quantitative comparison of effect levels to exposure estimates
    - Margin of Exposure approach
  - Sometimes requires more complex quantification (e.g., cumulative assessment)
  - Use of human biomonitoring data



Margins of Exposure

- Comparison of levels of human exposure for different age groups and subpopulations to levels associated with health effects (critical effect levels or Points of Departure: NO(A)EL, LO(A)EL, BMD)

$$\text{MOE} = \frac{\text{Critical Effect Level}}{\text{Estimate of Exposure}}$$

Interpretation of MOE

- Decision under S.64c based on adequacy of MOE to protect human in light of uncertainties
- **If MOEs don't appear to be adequate, consider further refinement! (iterative process)**
- Decision on adequacy of MOE involves consideration of several factors, including those commonly incorporated in uncertainty or safety factors used in derivation of regulatory values
- Draws on expertise developed through years of assessing various types of substances/datasets

Interpretation of MoE

Factors influencing interpretation of adequacy of MoE:

- Magnitude of margin
- Confidence in databases on effects and exposure
- Interspecies & inter-individual variability in sensitivity (sensitive sub-populations)
- Severity of effect
- Potential relation of critical effect to more severe effects
- Steepness of exposure-response curve
- Dose spacing in critical study
- Existence of lower bound on effect levels
- Potential for exposure from additional sources (concurrent exposures from multiple products)
- Others

Multiple MOEs

- MOE are derived for each likely exposure scenario
  - For intermittently used products, short term effect levels compared to shorter term exposure estimates during use of product or daily average estimates
    - E.g., paints, hobbies
  - For longer term frequently used products, longer term/chronic effect levels compared to long term exposures
    - E.g., skin lotion
  - For environmental media, average daily multimedia intake estimates or air concentrations are compared to chronic effect levels
- All MOEs are taken into consideration in risk characterization, with focus on values in which confidence is greatest (*N.B.: Not always the lowest effect level from dose-response characterization!)*
- **Refine as required!**

What MOEs Are Not

- MOEs derived in screening assessments are not:
  - A delineation of “safe” versus “unsafe”
  - An estimate of probability
  - A regulatory guidance value (but related)
    - MOE approach does not use default uncertainty factors or require the development of chemical specific uncertainty factors, but similar information taken into account in determining their adequacy

Human Biomonitoring Data (HBM)

- Amount of human biomonitoring data available increasing rapidly in Canada and elsewhere (e.g., Canadian Health Measures Survey, US National Health and Nutrition Examination Survey (NHANES))
- Chemical substances most commonly measured in breast milk, urine, whole blood and serum
- The use of HBM data in risk assessment allows for direct and a more precise assessment of risk
- Reflective of the absorbed dose into the human body and can provide a measure of integrated exposure from different exposure sources and routes
- Including the distribution of risk in a given population, incorporating individual variability in exposure and kinetics

Considerations for Use of Human Biomonitoring Data in Risk Assessment

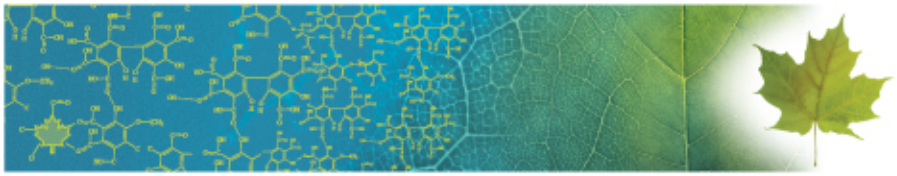
Within the context of CMP, there are a number of considerations prior to incorporation of Human Biomonitoring (HBM) data in human health risk assessment:

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

Use of HBM Data in CMP Risk Assessments

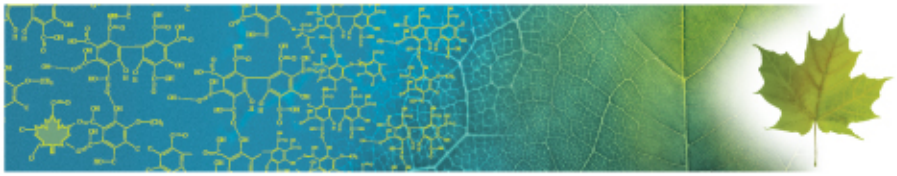
Use of HBM Data has evolved from qualitative to quantitative use including:

- 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



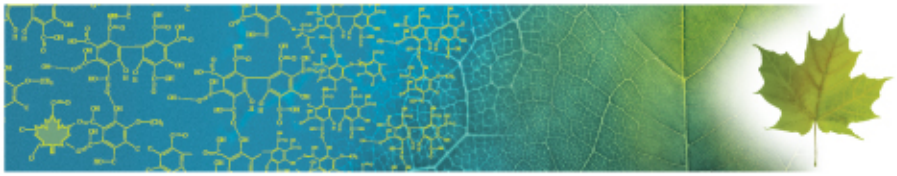
Uncertainties and Limitations of Using HBM in Risk Assessment

- 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 from national surveys 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
- Hazard data typically based on intake levels (mg/kg bw/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



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)



Characterization of Uncertainty in CMP Health Assessments

- Describe sources of uncertainty and potential impact on conclusion
  - Interspecies and intraspecies extrapolation (toxicokinetics/dynamics)
  - Uncertainty of analytical measurements
  - Nature or severity of the toxic effect
  - Size/type of population to be protected (sensitive/susceptible populations)
  - Quality of toxicological information
  - Database deficiencies
  - Assumptions related to models

- Identification of Data Gaps and Data Needs
  - Highlights where additional data can help to increase the precision and quality of the decision (reduce uncertainty)
  - Targeted research and monitoring and surveillance initiatives