Government of Canada / Gouvernement du Canada

Health Risk Assessment for Existing Substances

Chile Webinar

November 15, 2018

CHEMICALS MANAGEMENT PLAN

PLAN DE GESTION DES PRODUITS CHIMIQUES

Canada

Outline

- Risk Assessments Under CEPA
- Exposure Assessment
- Hazard Assessment
- Risk Characterization
- Governance Aspects
- Annex

Assessments under CEPA

- CEPA requires the assessment to determine if a substance is entering or may enter the environment in a quantity or concentration or under conditions that:
  - a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity
  - b) constitute or may constitute a danger to the environment on which life depends and/or
  - c) constitute or may constitute a danger to human life or health in Canada

- CEPA also stipulates that substances assessed to be harmful to human health and/or the environment ***must*** be risk managed.

Key Risk Assessment Principles & Objectives

- Protective of human health and the environment
- Incorporate weight-of-evidence and precaution
- Transparent process
- Based on sound science
- Flexible: Approaches must be able to accommodate:
  - various types of substances and groupings
  - varying amounts and types of information (e.g. data from analogues, predictive models to data rich)
  - emerging scientific knowledge and assessment approaches (e.g. use of biomonitoring data)

Principles for Gaining Efficiencies

- Fit For Purpose tiered assessments
  - "right-sized" approach – i.e., doing only what is required to make a sound decision
    - Using exposure data from DSL Inventory Update to inform level of assessment required
    - Aim to have complexity of the assessment commensurate with level of risk
- Adoption of existing hazard characterizations from international partners where available
  - Supplement with Canadian exposure scenarios to determine risk
  - Reduces the resources and time required to complete an assessment

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

Streamlined Assessment Approaches

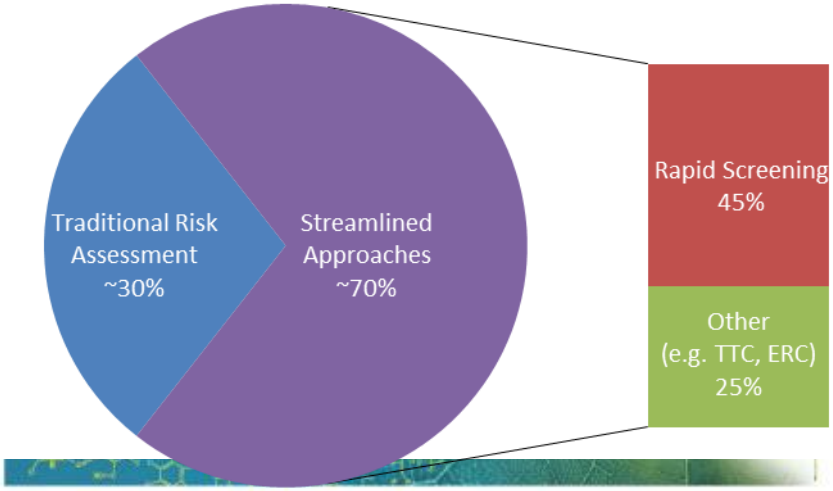
Rapid Screening Approaches

- Low Canadian commercial status
- Uses that not expected to lead to general population exposure
- Consideration of relevant ecological and hazard properties
- Applicable to substances and polymers (utilized approach in Polymer Rapid Screening I and II)

Human Biomonitoring approaches (Barium, Vanadium etc.)

- Low frequency of detection of biomarkers in humans, consideration of methodology (LOD, adequacy of biomarker etc.)
- Use of Biomonitoring guidance values (e.g. BE, HBM values)

Identification of substances which have already been assessed/managed previously



Approaches identifying substances where all uses in Canada are regulated under other acts (e.g. Pesticides, Pharmaceuticals)

Ecological Risk Classification Approach

- Establishes chemical profiles to provide a weight of evidence for hazard and exposure with the aim to develop a risk classification matrix for ecological receptors
- Uses several new approach methodologies (mode and mechanism of action, receptor binding, critical emission rate, margin of exposure)

Threshold of Toxicological Concern (TTC) Approach

- Principle of establishing a human exposure threshold value for chemicals below which there is a low probability of risk to human health (Kroes et al. 2004)
- Assigns a threshold value to a chemical based on structural features and compares this to an estimate of human exposure

External peer review of approaches and also open for public and stakeholder comment

* Accounts for, at minimum, one department utilizing a streamlined approach
** For both departments utilizing a streamlined approach on the same set of substances, proportion is ~ 50 % streamlined approaches vs. ~ 50 % traditional risk assessments

Health Risk Assessment - Principle Components

Exposure Assessment

Who is exposed, at what dose, through which route, how often or for how long?

Hazard Assessment

What type of adverse health effects may occur after exposure to a chemical?

Dose-Response Assessment

What are the health effects at different exposures?

Risk Characterization

A numerical estimate of risk, identification of key uncertainties.

Exposure Assessment

Overall Exposure Assessment Approach

- Tiered Approach
  - Focus on exposures of greatest concern or magnitude; strategic and targeted, not exhaustive
  - Refine estimates only as much as needed to determine that there is no concern at current levels of exposure
- Information Gathering
  - Goal is to compile a reasonable amount of information to support estimate of potential general population exposure in Canada
- Analysis of Information
  - Indirect exposure from food, breast milk, indoor air and dust (measured or modelled estimates compiled in multimedia intake table)
  - Direct exposure to consumer products (derive intake or concentration for each quantitative scenario identified using equations or models)

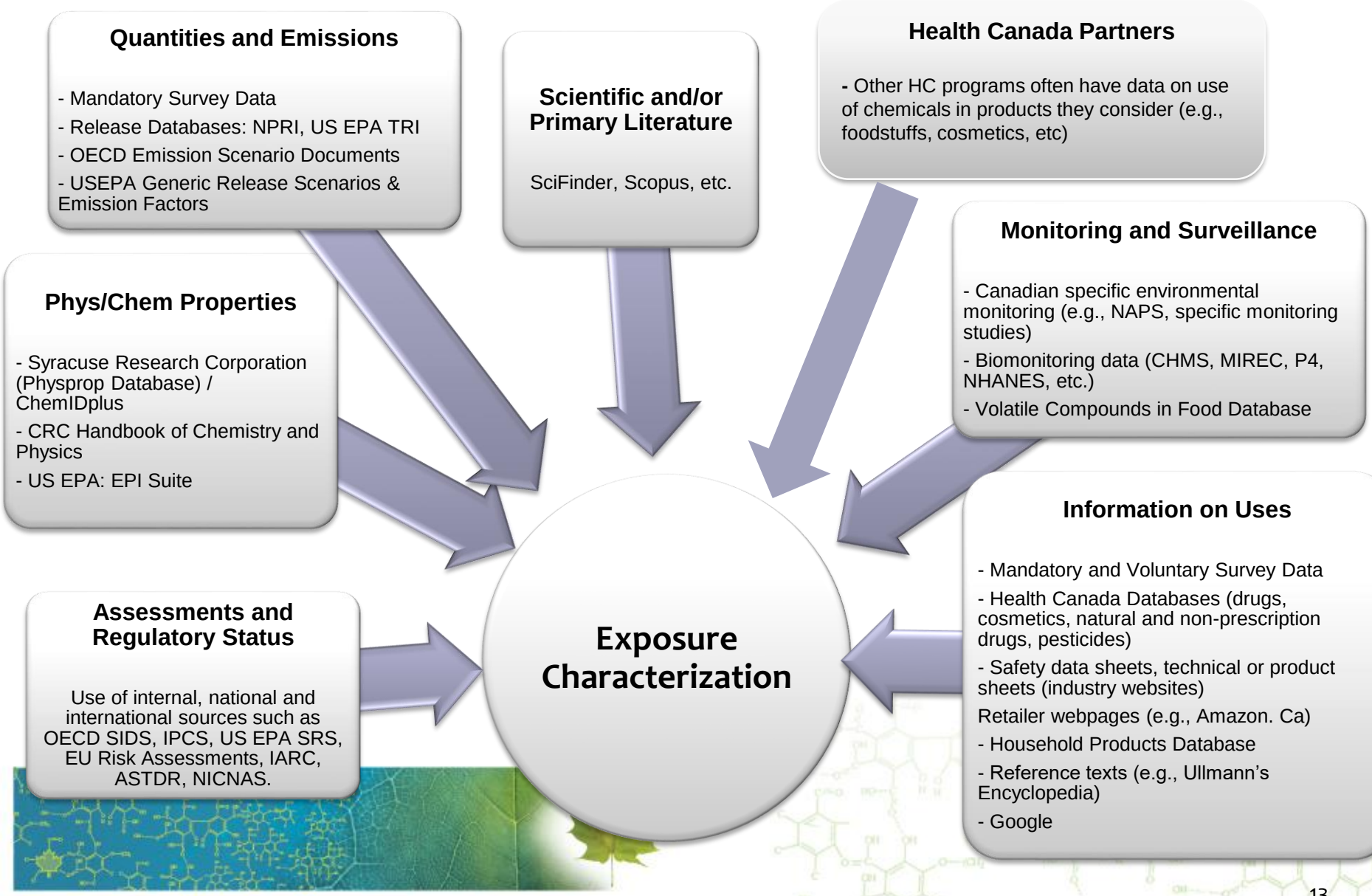
Exposure Assessments for Existing Substances

- Conservative estimates of population exposure (range of age groups considered) from general environment (multimedia), food and consumer products (where relevant) derived on basis of measurement data or modelled predictions:
  - Quantitative to extent possible (data dependent)
  - Serves to identify most important sources/routes of exposure
  - Aggregate exposure where appropriate
  - Characterize uncertainties and database confidence

Type of Information Required

- Physical–chemical properties
- Sources
  - Where substance is found and how much
  - Natural occurrence, industrial emissions, volumes in Canada, and elsewhere
  - Environmental monitoring data (food, breast milk, drinking water, indoor/outdoor air, soil, dust)
- Uses
  - How is it used? What is its function?
  - Known Canadian uses/applications, global uses/applications considered as well
  - Consumer products, including mixtures, products or manufactured items
  - Food flavourants/food additives/food packaging
  - Natural health products and drugs (non-medicinal ingredients)
  - Focus on uses of substance by the general population, not occupational uses
- Human biomonitoring data
  - Requires pharmacokinetic data
- Dermal absorption data

Sources of Exposure Data



Exposure Data Gathering Tools

Exposure Problem Formulation Database (ePFDB)	Exposure Data Gathering Strategy (EDGS)	Safety Data Sheet Search Tool
• Microsoft Access database • Starting point for data gathering • Info on volume in commerce, use from Canada and U.S. • Biomonitoring data • Environmental monitoring data • International Activities • Some use information, etc.	• Web-based application tool that queries multiple web resources simultaneously and presents the results/links • Includes typical sources identified for biomonitoring, phys-chem, products and food, environmental media, international assessments and activity	• Web-based automated tool, focusing on Canadian retailers and Walmart.com

❖ Tools developed in-house, tailored to meet our specific needs

Environmental Media and Food

Rank relevant information for general population exposure:

- Geographic: Canada > US > Elsewhere
- Temporal : Recent (< 5 years) > Older
- Exposure may be modelled

Modelling:

– Several models are available free online to model environmental media exposure in the absence of data:

- Fugacity models for environmental distribution
  – US EPA EPISuite, CEMC ChemCan
- Screen 3 (air dispersion model) or AERMOD, US EPA's E-FAST (e.g., point source, down the drain)
- Additional tools always being developed for consideration

Environmental Media and Food

Multimedia intake estimates:

- In–house spreadsheet that automatically calculates intakes for environmental media for all age groups
- Identifies populations with highest exposures and principle sources

$$Intake = \frac{C\ x\ IR\ x\ EF}{bw}$$

Where:

C = concentration of the contaminant in air (µg/m^3), water (µg/L), soil/dust (µg/kg), or food (µg/g)

IR = amount of air a person breathes in a day (m^3/day), amount of water a person drinks in a day (L/day), amount of soil/dust a person ingests in a day (mg/day), amount of food a person eats in a day (g/day)

EF = exposure factor, indicates how often the individual has been exposed to the contaminant over a day, a year or a lifetime.

*EF may not be required in all situations (e.g., if just want to know daily intake can just use daily intake rate such as ingest 1.5 L of water per day or 16.2 m^3 of air per day)

Standard Values and Intake Table

Route of exposure	Estimated intake (µg/kg-bw per day) of (substance name) by various age groups							
	0-6 months			0.5-4 years	5-11 years	12-19 years	20-59 years	60+ years
	breast fed	formula fed	not formula fed					
Ambient air	0.00			0.00	0.00	0.00	0.00	**0.00**
Indoor air	0.00			0.00	0.00	0.00	0.00	**0.00**
Drinking water	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.00**
Food and beverages	0.00	0.00	0.00	0.00	0.00	0.00	0.00	**0.00**
Soil	0.00			0.00	0.00	NA	NA	**NA**
Total intake	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**

Exposure Factor	Age Groups							Reference
	0-6 mths		6 mths - 4 years	5-11 years	12-19 years	20-59 years	60+ years	
Body Weight (kg)	7.5		15.5	31.0	59.4	70.9	72.0	Health Canada 1998
Inhalation Rate (m^3/day)	2.1		9.3	14.5	15.8	16.2	14.3	Health Canada 1998
Drinking Water Intake (L/day)	Breast Fed	0	0.7	1.1	1.2	1.5	1.6	
	Formula Fed	0.3 or 0.8						
	Not Formula Fed	0.8						
Soil Ingestion Rate (mg/day)	**30**		**100**	**65**	**30**	**30**	**30**	

Exposure Scenarios - Products

- Organize information to determine:
  - Key drivers of exposure
  - Representative scenarios (products used by consumers)
  - Which scenarios to address qualitatively and quantitatively

- Derive an intake (mg/kg-bw/d) or concentration (e.g., mg/m^3) for each quantitative scenario identified
  - Using models or equations
  - Consult guidance materials and previous assessments
    - Keep a record, including rough calculations for lesser scenarios, to ensure they result in lower expected exposure than the chosen representative scenarios.
  - Refine scenario inputs, if necessary (i.e., if determined to be too unrealistic).

Modelling Consumer Product Exposure

- Models used to estimate exposure via consumer products [available free online]
  - ConsExpo (RIVM)
  - Consumer Exposure Model or CEM (US EPA)
  - IH Mod (AIHA)

Information Needed to Run Exposure Models

Product Information

- Concentration of substance in product
- Routes of exposure (oral, dermal, inhalation)
- Populations exposed (children, adults)
- Amount of product used
- Other (mass transfer rates, release area, etc.)

Scenario Information

- Frequency of use
- Product amount
- Duration of use
- Information on room (volume, ventilation rate)
- Anthropometric data (inhalation rates, body weights, etc.)

Sources of Information

- US EPA Exposure Factors Handbook
- ConsExpo Fact Sheets
- Health Canada – compiled defaults for personal care products and household cleaning products
- Product information sheets or label instructions
- Other (SCCS, scientific literature, etc.)

Hazard Assessment

Overall Hazard Assessment Approach

- Tiered approach:
  - Start with conservative assumptions and refine as necessary (may be limited by data availability)
- Key steps in preparation of hazard assessment
  1. Information gathering:
     - Chemical specific empirical information when available
     - Data gaps filled with predictive tools
       - Computer models (“in silico” approaches)
       - Chemical analogues for “read-across” purposes
  2. Organization of information
  3. Analysis of information
     - Identification of critical effects
     - Identification of critical effect levels

Information Gathering Sources & Tools

- HC Partners
  - Call-out to other program areas within HC
  - Often have access to data specific to their area (e.g., cosmetics) that wouldn't be captured by our search strategies
- SAR Search
  - Tool that allows searching for key words in published SARs
  - Gains efficiencies and ensures consistency
- Contractors
  - Frees up in-house staff
  - Generally more success with hazard information
- HDGS (Hazard Data Gathering Strategy)
  - Web based search application developed in-house that simultaneously queries multiple web resources for relevant information and presents the results/links

Sources Consulted by HDGS

Static Resources

- Canada DSL
- ECHA Registered Substances
- ECHA Inventory
- Health Canada Drug Product Database (DPD)
- Health Canada Licensed Natural Health Product Database (LNHPD)
- ATSDR (Agency for Toxic Substances & Disease Registry) Toxicological Profiles
- EPA ToxCast/Tox21 Substances
- EU Pesticides Database

Live Resources

- Health Canada Natural Health Products Ingredients Database (NHPID)
- eChemPortal
- TOXNET
- Scopus
- PubMed
- PubChem
- IARC Monographs
- NTP
- CCOHS RTECS
- IPCS INCHEM
- JECFA Monographs and Evaluations
- CosIng
- ToxRefDB
- ToxCast
- EDSP21
- Institute of Medicine
- US FDA
- Chemical Data Access Tool (CDAT)
- US EPA Pesticides
- EU Pesticides Database
- Australian IMAP
- 23 commonly referenced toxicology journals

Determination of Critical Effects

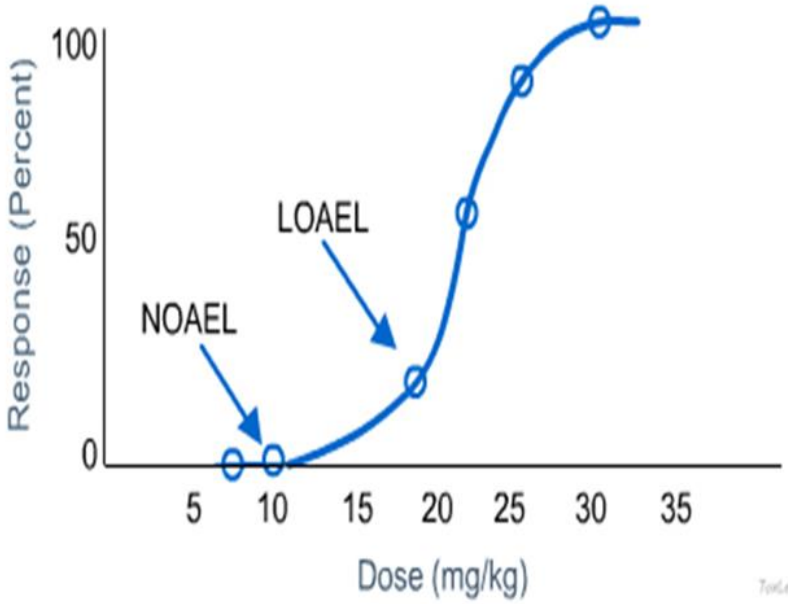
- Organize study data
  - e.g., by focus of study (cancer, genotoxicity, developmental, etc.), route, duration, species, etc.
- Look for patterns in effects data – weight and strength of evidence
  - Nature of effects, target organs/systems reported in multiple studies, in multiple species
  - Did incidence/prevalence or severity of response increase with increasing dose/concentration? (examine dose-response)
  - What effects are repeatedly observed at the lowest dose/concentration?
  - Relative weighting of studies, from conservative perspective
  - Integrate observed effects with supporting information (e.g., metabolism, precursor effects)

Determination of Critical Effects

- Evidence for endpoints of high concern considered early:
  - Carcinogenicity and genotoxicity
    - look for indications of genotoxic carcinogenic mode of action *in a screening context*
  - Reproductive and developmental toxicity
- Consider evidence for human relevance of observed effect, taking into consideration existing knowledge *in a screening context*
- Consider multiple study designs vs. population exposure scenarios
  - if food is key source, select longer term oral study if available
  - if product involving dermal contact used occasionally, short term dermal study is ideal

Determination of Critical Effect Levels

- Consider multiple endpoints across the entire database to establish critical effects and critical effect levels/Points of Departure (NO(A)ELs, LO(A)ELs, BMDs)
  - What dose causes an adverse effect on endpoint of concern?
  - Author reported effect levels generally accepted



Obtained from:
toxlearn.nlm.nih.gov

Predictive Tools for Hazard Assessment

Commercial

- *CASE Ultra Tox*
- *DEREK Nexus*
- *Leadscope Model Applier*
- *Oasis Times*
- *ACD Percepta*
- *ChemBioOffice*
- *GastroPlus*

Non-commercial

- *OECD QSAR Toolbox*
- *Toxtree*
- *OncoLogic*
- *VEGA Caesar*
- *Analog Identification Methodology (AIM)*
- *HESS*

Cheminformatics tools

- *Leadscope Hosted - chemical data miner, clustering*
- *Knime – cheminformatics and workflow builder*

Read-Across

	Chemical 1	Chemical 2	Chemical 3	Chemical 4	
Structure	Structure 1	Structure 2	Structure 3	Structure 4	
Property 1	Y →	N	Y →	N	SAR/Read-across
Property 2	Y →	N	N ←	Y	Interpolation
Property 3	N ←	Y	Y →	N	Extrapolation

Y = known/existing data
N = unknown/missing data

Read-Across: Endpoint information for one chemical (the source chemical) is used to predict the same endpoint for another chemical (the target chemical), which is considered to be "similar" in some way (usually on the basis of structural similarity).

Risk Characterization

Risk Characterization

- Qualitative or semi-quantitative, for example:
  - If substance not likely to be found in the environment based on physical and chemical properties or low quantities in use (i.e., exposure is minimal or negligible)
  - If data indicate that dermal absorption is very low or unlikely, or if substance is very volatile may not be relevant to quantify risk via the dermal route
- Quantitative
  - ***Margin of Exposure (MOE)****: 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)*

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

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!)*

Interpretation of MOE

- Decision of whether substances is of concern for human health or not is based on the adequacy of MOE to protect humans 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

Interpretation of MoE

Factors influencing interpretation of adequacy of MoE:

- Magnitude of margin
- Confidence in databases on effects and exposure; impact of uncertainties on direction of margin
- 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

Characterization of Uncertainty

- Indicate the overall confidence and uncertainty in the exposure and hazard assessment based on
  - Quality and amount of relevant data incorporated
  - Identify any data gaps critical to the assessment
  - Describe any important issues with studies used to estimate exposure (e.g., use of limited data from other countries) or characterize hazard (e.g., uncertainty regarding species differences in sensitivity)
  - Key assumptions inherent in models and defaults

- Specify whether the uncertainties could result in an underestimation or overestimation of risk

Consultation & Review Process

- Internal:
  - Other scientists within ESRAB
  - Other HC program areas implicated in assessment (e.g., Consumer Products Safety Directorate, Health Products and Food Branch, etc)
  - HC Research Community
  - Several layers of HC management
  - Legal Services

- External:
  - International engagement on technical issues feed into assessment approach
  - Publication of Science Approach Documents to obtain broad input
  - Expert peer review
  - Science Committee input on specific issues

Gracias!

Thank You!

ANNEX

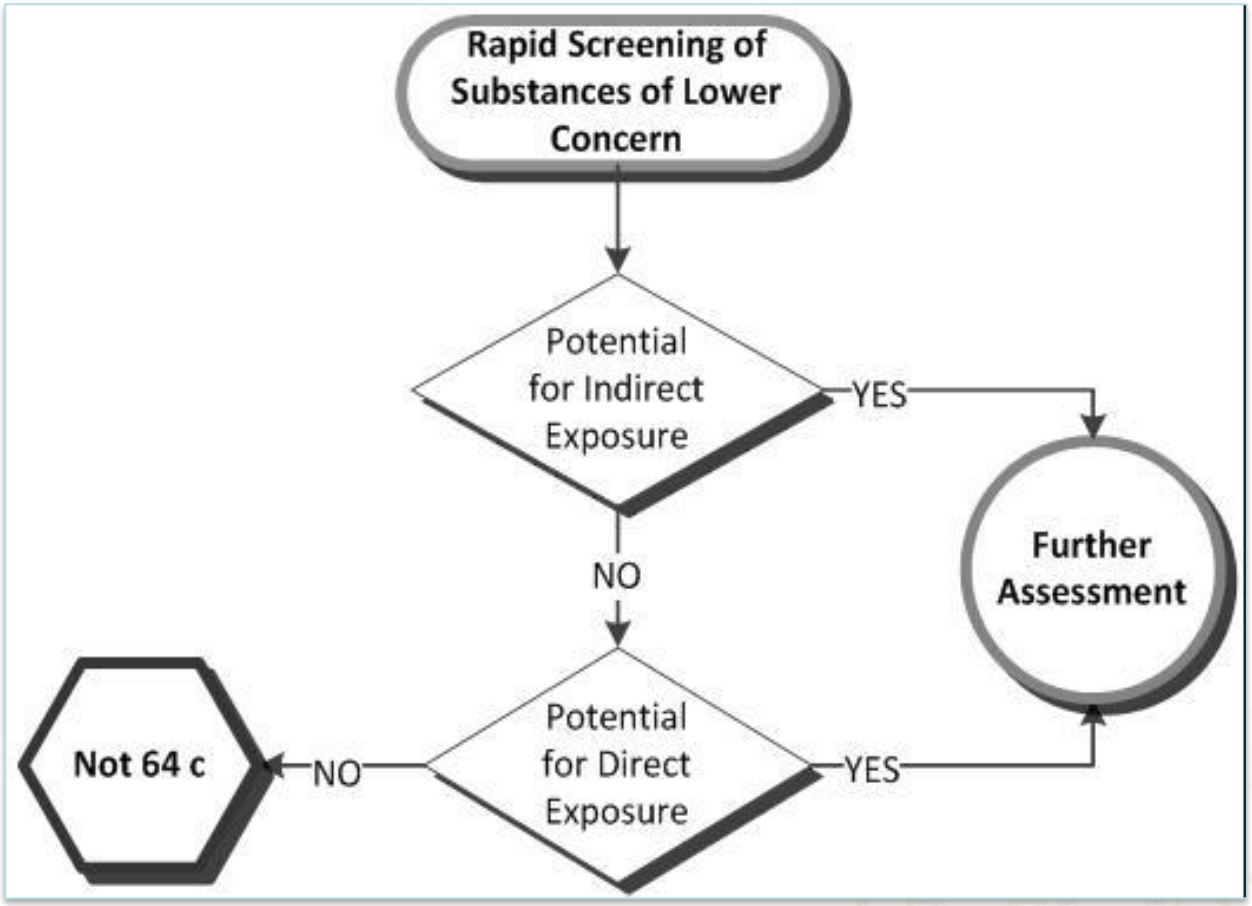
Rapid Screening Approach

- A series of qualitative and quantitative steps to evaluate the likelihood that a substance may cause harm based on conservative exposure estimates

- Outcomes:
  - Substance identified as requiring further assessment if at any time during the process it appears to present potential harm, OR
  - Concluded as unlikely to meet the criteria under CEPA 1999 if it passes each step successfully

- As the CMP continued:
  - This approach was further used for substances of lower concern identified from Phase 1 and 2 of the DSL Inventory Update
  - Allows for substances of low concern to be addressed efficiently

Rapid Screening



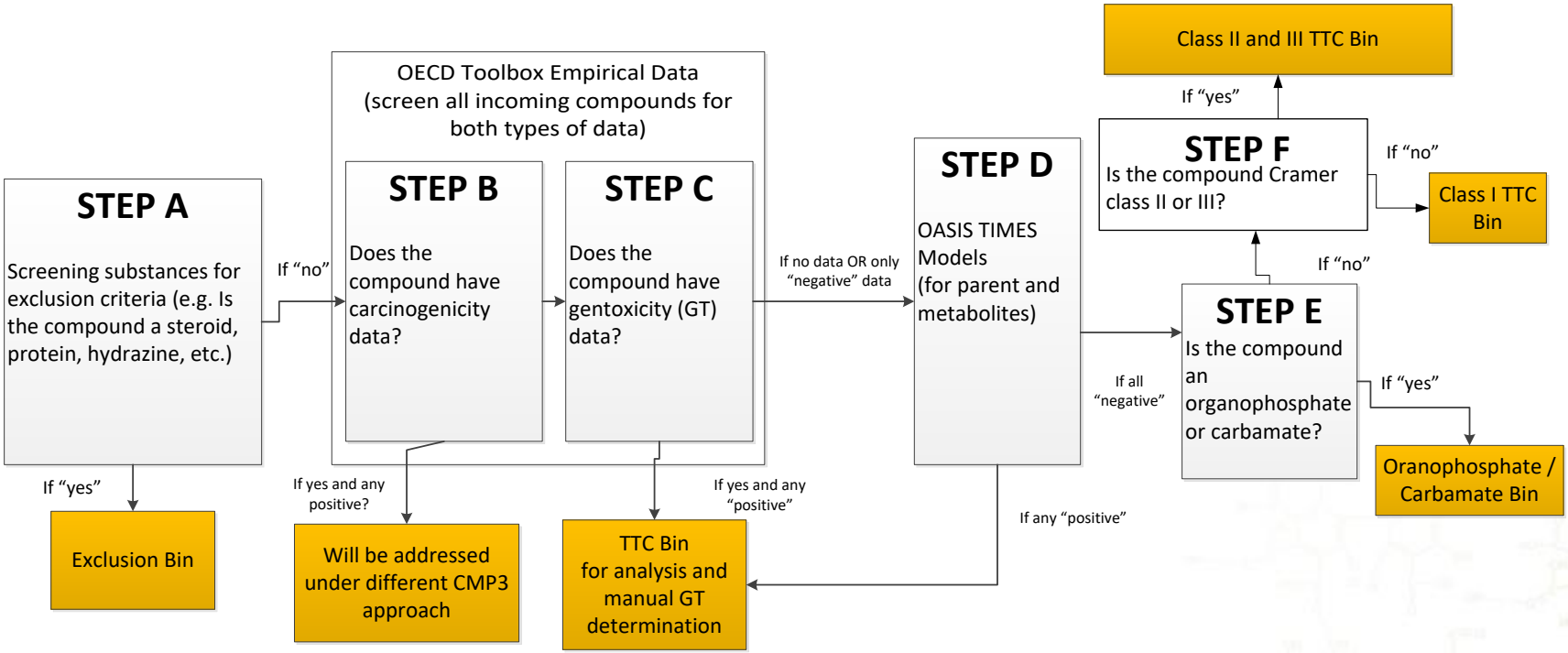
Threshold of Toxicological Concern (TTC) Approach

- The Threshold of Toxicological Concern (TTC)-based Approach for Certain Substances is an example of a fit-for-purpose human health approach
  - Applied to substances for which exposure to the general population is expected to be limited
  - Incorporates conservative appropriate for screening substances out
- Based on the principle of establishing human exposure threshold values for chemicals, below which there is a low likelihood of risk to human health (Kroes et al. 2004)
- Threshold values have been established for substances with genotoxic alerts and each of three chemical classes (called “Cramer” classes)
- The TTC is compared to an estimate of human exposure, and substances which have exposure below the assigned TTC value are considered to be of low concern for human health

Chemical class	TTC values (µg/kg bw/day)
Cramer class I	30
Cramer class II	9.0
Cramer class III	1.5
Genotoxic compounds	0.0025

TTC Approach

- Substances are screened for relevant empirical/predictive health effects data and classified as potentially genotoxic or as their respective “Cramer” structural class with corresponding threshold value



Links to More information

- **Chemicals Management Plan**
  - http://www.chemicalsubstanceschimiques.gc.ca
- **Categorization**
  - http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=5F213FA8-1&wsdoc=1695F8D0-5CC4-EDA1-AF63-6F23A94064DD
- **Categorization Guidance and Results**
  - http://webnet.oecd.org/ccrweb/Default.aspx
- **Rapid Screening**
  - http://www.chemicalsubstanceschimiques.gc.ca/plan/approach-approche/rapid-eng.php
- **Petroleum Sector Stream Approach**
  - http://www.chemicalsubstanceschimiques.gc.ca/petrole/index-eng.php

Links to More information (cont.)

- ***Canadian Environmental Protection Act 1999***
  - http://laws-lois.justice.gc.ca/eng/acts/C-15.31/
- **Chemical substances website**
  - http://www.chemicalsubstanceschimiques.gc.ca/approach-approche/index-eng.php
- **CMP Progress Report (bi-annual publication)**
  - http://www.chemicalsubstanceschimiques.gc.ca/plan/progress_report-rapport_etape-eng.php
- **Mandatory survey notice under section 71**
  - https://www.canada.ca/en/health-canada/services/chemical-substances/canada-approach-chemicals/information-gathering.html
- **Two-year rolling risk management activities and consultations schedule**
  - https://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=8727ECCE-1
- **Report of the Standing Committee on Environment and Sustainable Development (ENVI)**
  - http://www.ourcommons.ca/content/Committee/421/ENVI/WebDoc/WD10002919/421_ENVI_reldoc12_PDF/DeptOfTheEnvironment-e.pdf

Links to More information (cont.)

- Environmental Exposure Models
  - CEMC's ChemCan Fugacity Model: http://www.trentu.ca/academic/aminss/envmodel/models/CC600.html
  - U.S. EPA's Screen 3 (air dispersion model) includes links to other air models: https://www3.epa.gov/ttn/scram/dispersion_screening.htm#screen3
  - U.S. EPA's E-FAST: https://www.epa.gov/tsca-screening-tools/e-fast-exposure-and-fate-assessment-screening-tool-version-2014

- Consumer Product Exposure Models
  - U.S. EPA's Consumer Exposure Model (CEM): https://www.epa.gov/tsca-screening-tools/cem-consumer-exposure-model-download-and-install-instructions
  - U.S. EPA's Wall Paint Exposure Model (WPEM): https://www.epa.gov/tsca-screening-tools/wall-paint-exposure-assessment-model-wpem
  - American Industrial Hygiene Association IH Mod (and other tools): https://www.aiha.org/get-involved/VolunteerGroups/Pages/Exposure-Assessment-Strategies-Committee.aspx