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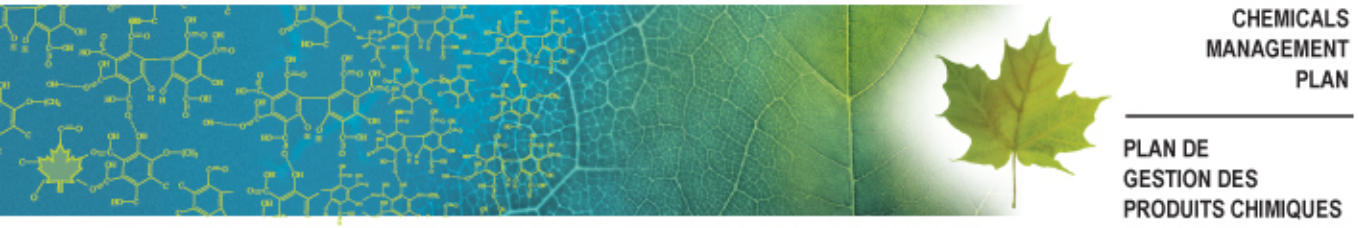
Risk Assessment of Existing Substances Under the CMP: Principles and Approaches

Health Canada – PAHO Workshop

Lima, Peru

November 8-10, 2016



CHEMICALS MANAGEMENT PLAN

PLAN DE GESTION DES PRODUITS CHIMIQUES

Canada

Outline

- Basic Principles and Objectives
- Assessment Activities
  - CMP Phase 1
  - CMP Phase 2
  - CMP Phase 3

Basic Principles & Objectives

- Protective of human health and the environment;
- Incorporates weight-of-evidence and precaution as required under CEPA 1999;
- Transparent process
- Based on sound science

Flexible Approaches

- Flexible: Approach must be able to accommodate substances and groupings with varying amounts and types of information, and emerging scientific knowledge and assessment approaches

- Assessment methods adaptable to a range of substances from data poor…
  - use of information from related chemicals (i.e. analogues)
  - use of models
    - release and exposure estimates
    - toxicity predictions

…to data rich

- use of information on differences in sensitivity between species
- environmental monitoring data

Canada's Chemical Management Plan - Phase 1 (CMP1)

- Health Risk Assessment Initiatives under CMP1
  - The Ministers' Challenge (~200 high priority substances (eco and/or health))
  - Rapid screening (~1000 substances)
  - Petroleum Sector Stream Approach (~160 substances)

Intent of the Challenge

The Ministers intend…

- "to develop or implement measures to assess and manage the risks posed by certain substances"
- "to identify industrial best practices in order to set benchmarks for risk management, product stewardship, and virtual elimination"

The Ministers consider…

- "Evidence that a substance for which the critical health effect is assumed to have no threshold – i.e. a genotoxic carcinogen – it is assumed that there is a probability of harm to human health at any level of exposure, and therefore indicates that the substance meets the criteria for "toxic" to human health in CEPA 1999"
- "Evidence that a substance exhibits carcinogenicity, mutagenicity, developmental toxicity, or reproductive toxicity, and a high likelihood of exposure to individuals in Canada, indicates that the substance meets the criteria for "toxic" to human health in CEPA 1999"

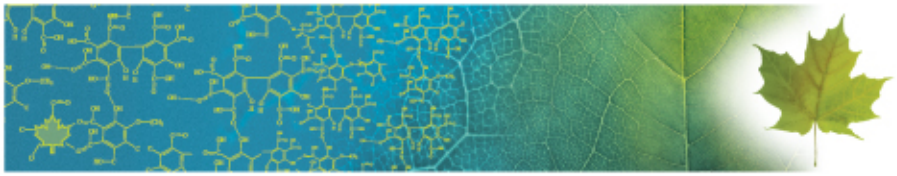
High Health Priorities

Sixty–six (66) substances were considered High Health Priorities on basis of:

- Significant potential for exposure based on application of Simple Exposure Tool
  - Greatest Potential for Exposure (GPE)
  - Intermediate Potential for Exposure (IPE)

- AND -

- Known high hazard based on classification systems of other national/international agencies (Simple Hazard Tool)
  - Carinogenicity
  - Genotoxicity
  - Reproductive/Developmental toxicity



Challenge Screening Health Assessments

- Therefore, Challenge screening health assessments prepared in light of these stated intents.
- Process and format of assessment designed to “fit the purpose” of Challenge
- Yet still include principle components of health risk assessment

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

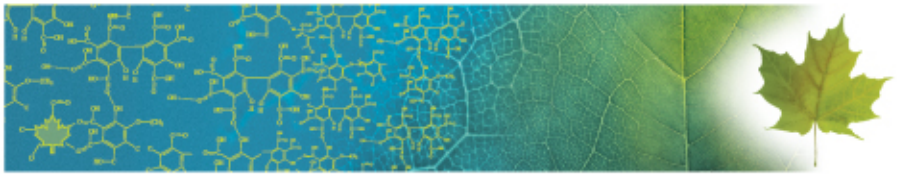
What are the health effects at different exposures?

Risk Characterization

A numerical estimate of risk, identification of key uncertainties.

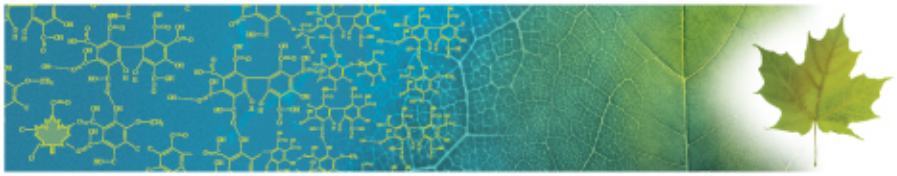
Challenge Screening Assessments - Exposure

- Conservative upper bounding estimates of population exposure from general environment (indoor & outdoor air, drinking water, soil & dust, food) and consumer products (where relevant)
  - Quantitative to extent possible (data dependent)
  - Serves to identify most important sources/routes of exposure
  - Based on data provided in s71 responses from industry, open literature, HC programs, federal and provincial monitoring programs, MSDS, etc.
  - Canadian data usually given priority, but often not available
  - Empirical data preferred, but models used as considered appropriate (ChemCan, ConsExpo, etc.)



Challenge Screening Assessments - Hazard

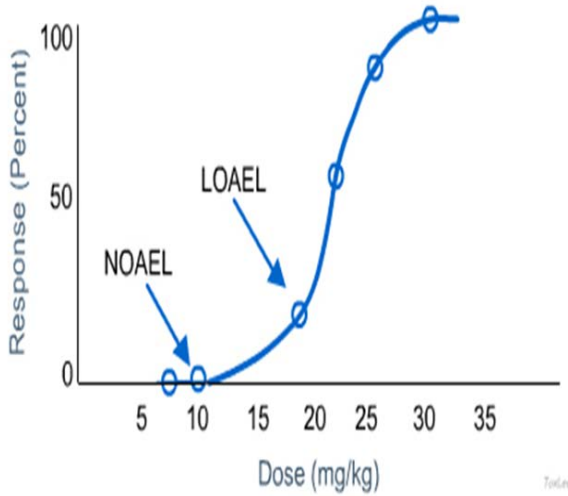
- Generally, national/international classifications that were basis for categorization will be used as the basis for characterizing the hazard (critical health effects)
  - Capitalizes on work done internationally; obviates necessity to re-examine large complex datasets
  - Ensures consistency/harmonization with other agencies
- Consideration also of other health effects of potential concern beyond the basis for the classification based on evaluation of available information in a screening context
- Based on toxicological and epidemiological data; predictive models or knowledge of similar compounds considered as required
- Literature searches conducted to identify recent data and studies outside scope of classification assessment



Challenge Screening Assessments - Dose-Response

What dose causes an adverse effect or endpoint of concern?

- Point of Departure from previous assessment
- Examination of incidence and severity of effect at doses tested
  - NOAEL
  - LOAEL
  - BMD (dose associated with specific rate of response)



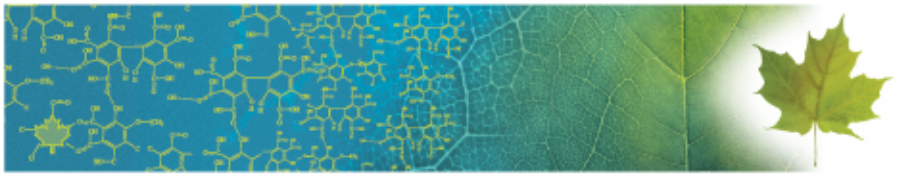
Obtained from: toxlearn.nlm.nih.gov

Risk Characterization

- Approach depended on nature of critical effect (threshold vs. non-threshold)
  - Recall Ministers' intent re. non-threshold effects
  - Conservative approach to determining whether a threshold existed (relied heavily on existing assessment conclusions)
- Quantification of risk generally involved a Margin of Exposure approach
  - Comparison between quantitative characterization of hazard (Point of Departure/Critical Effect Level) and upper bounding estimate of population exposure

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

  - Consideration of adequacy of margins of exposure to protect health in light of uncertainties



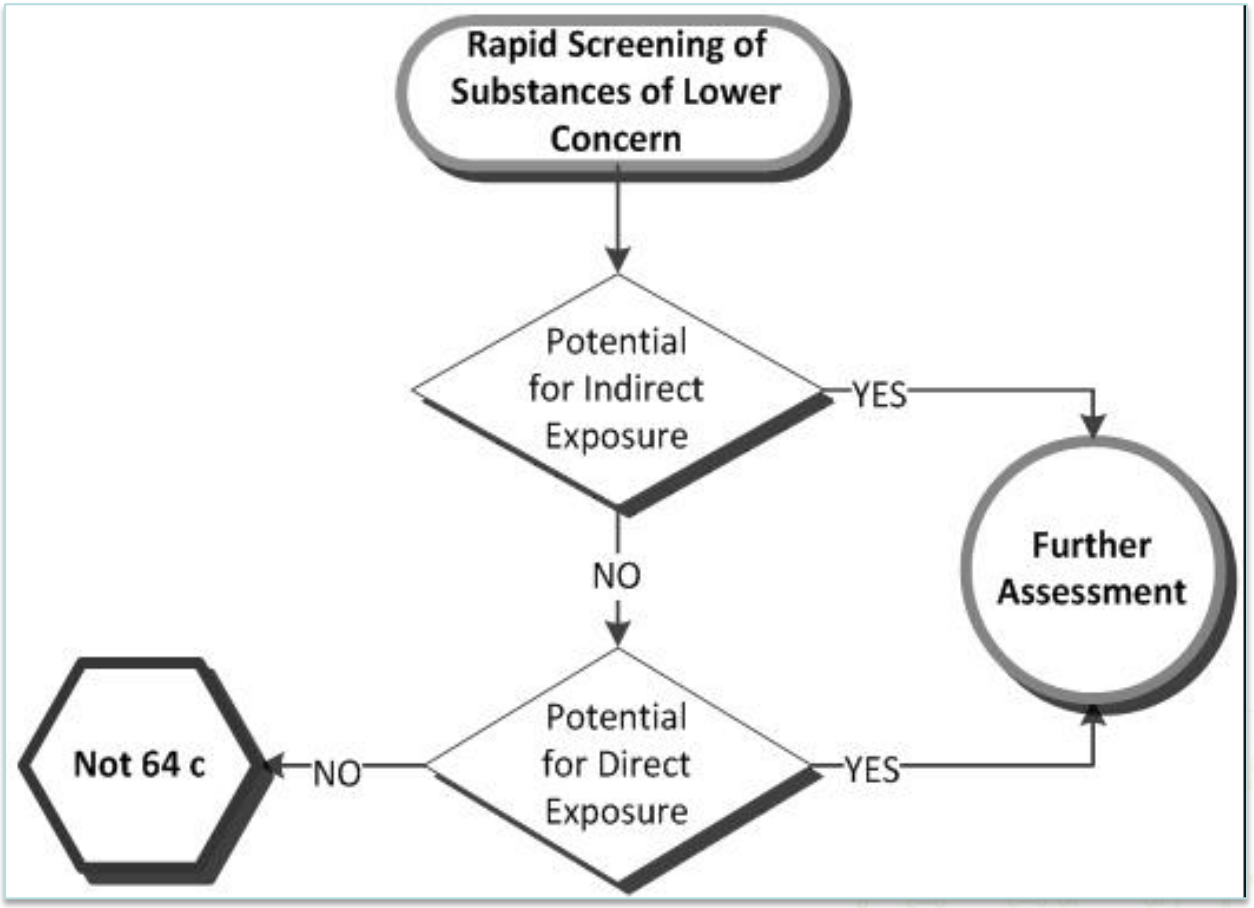
Rapid Screening of Substances of Low Concern (Rapid Screening 1)

- Candidate substances
  - Met categorization criteria as being inherently toxic (ecological) and either persistent or bioaccumulative (but not both),
  - In Canadian commerce in low quantities (≤1000 kg), based on 1986 data, and were therefore expected to be of lower concern
  - None of the substances met categorization criteria for human health

- Substances were assessed for ecological concerns first

- Those substances that did not require further assessment based on ecological concerns were evaluated to determine whether a given substance is of potential concern from a human health perspective
  - A key element of characterization of potential risk for human health is determination of potential for direct exposure to the general population

Rapid Screening



Petroleum Sector Substances

- Petroleum stream
  - Opportunity to use sectoral expertise and work with industry and others to deal with a large number of substances in an innovative and efficient way
- Focused on data gathering and grouping similar substances for assessment and management while including synergies with other existing initiatives such as best management practices, spill prevention, environmental emergencies etc.
- Grouped substances based on similarity in properties (e.g. : Low Boiling Point Naphthas) and on increasing complexity of exposure scenarios
  - Stream 1 – Site restricted: don't leave petroleum facilities (e.g. process intermediates)
  - Stream 2 – Industry restricted: transferred between industrial facilities but do not reach public in form acquired (e.g. fuel blending component)
  - Stream 3 – Fuels (e.g. aviation fuels, home heating oil)
  - Stream 4 – Present in consumer products, probability of direct exposure (e.g. petrolatum)

Canada's Chemicals Management Plan - Phase 2 (CMP2)

- Building upon success and lessons learned of the first phase of CMP, the second phase was announced on October 3, 2011
- Key Assessment Activities under CMP2 included:
  - Substance Groupings Initiative
  - Polymers
  - Pesticidal use only
  - Additional Rapid Screening approaches
  - Cumulative Exposure
  - Other (Metals, UVCBs)

Substance Groupings Initiative

- A key component of CMP2:
  - Assessing and managing, where appropriate, potential health and ecological risks associated with 9 groupings of substances
  - Substance groupings were based on structural or functional similarities and assessment or management efficiencies, timing of international actions and stakeholder engagement

Substance Groupings Initiative

- Aromatic azo- and benzidine based substances (358)
- Substituted diphenylamines (SPDAs) (13)
- Cobalt containing substances (50)
- Methylenediphenyl diisocyanates and diamines (MDI/MDA) (7)
- Certain internationally classified substances (6)
- Certain organic flame retardants (10)
- Selenium containing substances (29)
- Phthalates (14)
- Boron containing substances (15)

Cumulative Risk Assessment

- Cumulative risk is the combined exposure to multiple substances with a common mode of action

- **Experience To Date and Moving Forward**
  - A cumulative risk approach was applied to the Phthalates Substance grouping.
  - Input from CMP Science Committee (November 2015) is informing our path forward
  - With a view to broadly accepted guidance, Canada is co-leading a guidance project on the combined exposure to multiple chemicals under the OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology

Cumulative Risk

- Progresses beyond a simple “group” assessment, where groups are defined by structure
- Attempts to deliver a more realistic assessment by answering the question “What happens with exposure to multiple chemicals **with the same toxic mode of action** (MoA)?” (Same MoA is a pre-condition)
- Chemicals with similar molecular structures often have similar MoA, but may have **different toxicological potency**
- Cumulative assessment attempts to add toxicity from substances that exert **the same toxic effect**. Exposures must be adjusted for **differences in potency** before they are added together**.**
  $100 = $20x5 = $10x10 = ($20x2 + $10x6)
- It’s more complicated than adding dollars to get to a purchase price
- This is an area where *in vitro* or High Throughput screening can help confirm the MoA and evaluate potency of different substances

Rapid Screening 2

Rapid Screening of Substances from Phase One of the *DSL* Inventory Update

- Based on information submitted pursuant to section 71 of CEPA 1999 regarding commercial activity in Canada (2008 calendar year)
- 140 of 500 surveyed CMP priority substances were considered candidates for rapid screening based on as being reported in commerce in Canada at ≤ 1000 kg/year
- All 140 substances were evaluated for both ecological and human health concerns
- Most substances (~85%) were concluded to not meet the criteria for CEPA 1999 “toxic”
- The remaining substances were identified as requiring further assessment

Rapid Screening 3

Rapid Screening of Substances from Phase Two of the *DSL* Inventory Update

- 870 of the approximately 2700 inanimate substances surveyed were identified for application of a rapid screening approach because they were reported to be in Canadian commerce at a total quantity of ≤ 1000 kg/year (2011 calendar year)
- All substances were evaluated for both ecological and human health concerns
- The draft assessment proposes that ~70% of substances do not meet any of the criteria set out for “toxic” under CEPA 1999
- The remainder were identified as requiring further assessment

Pesticide Uses Only Substances

- Nineteen CMP prioritized substances registered as active ingredients in pest control products under the *Pest Control Products Act* (PCPA)
- Pesticidal applications of these substances were evaluated for environmental and human health concerns by the Pest Management Regulatory Agency of Health Canada
- Based on information collected in response to Phase One and Phase Two of the DSL inventory update and other available information on substance use, it was determined that the 19 substances have uses in Canada that are limited to pesticide applications
- As a result, these 19 substances were concluded to not be harmful to the environment or to human health as per the CEPA 1999 criteria

Polymer Approach

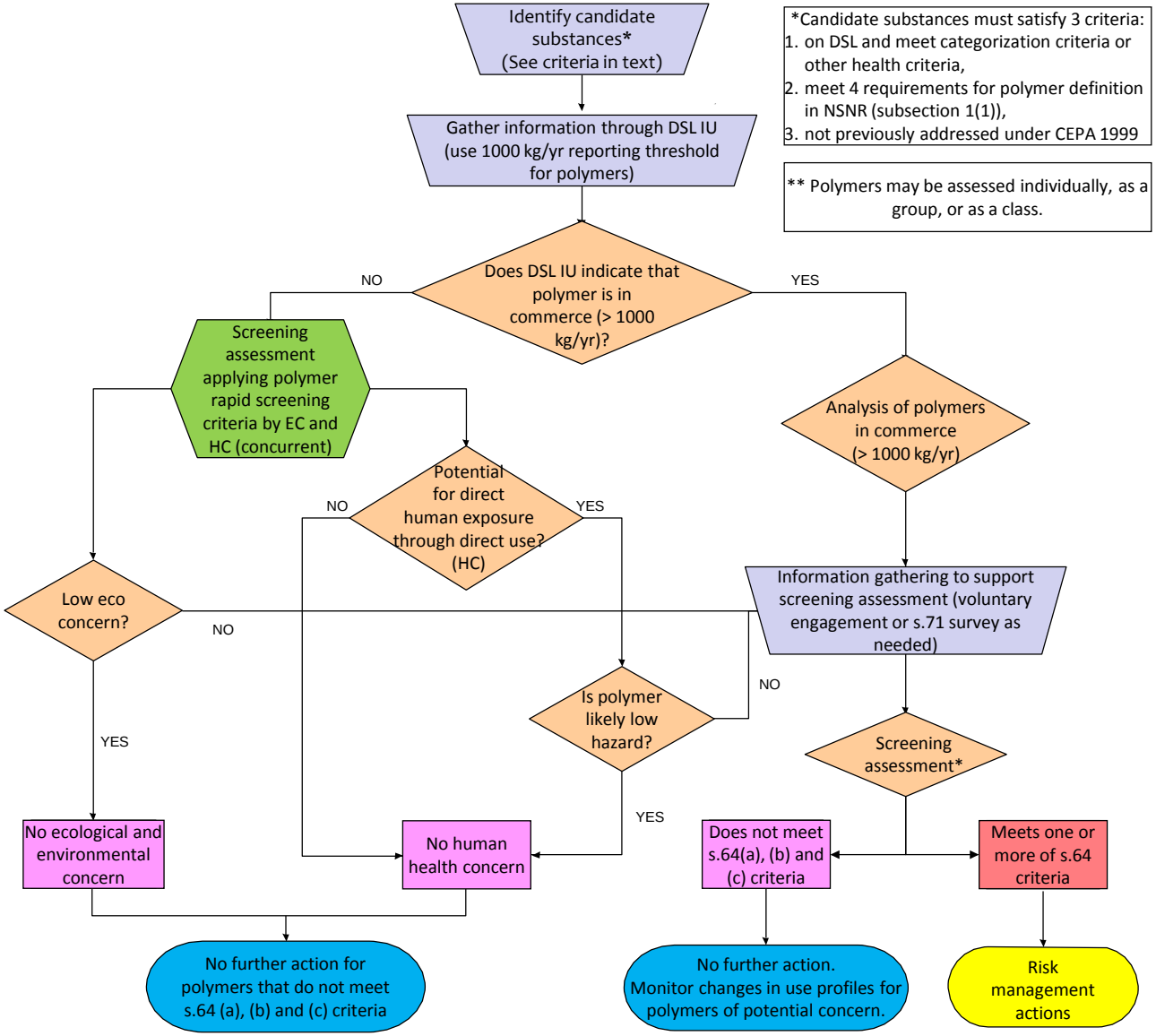
- Polymers account for a significant portion of the 4,300 priorities identified during Categorization (~14%)

- Polymers are a unique class of substances, where the same CAS RN can be used to describe substances that have different molecular weights, toxicity, and physical chemical properties

- Approach for polymers was developed and posted on the Chemical Substances website

  http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=42550DBF-1

Approach to Assessment of Polymers



Polymer Approach

- Using information from the DSL Inventory Update, polymers are triaged
  - Amount in commerce
  - Direct population exposure
  - Likelihood of low hazard
- Basis for low hazard:
  - a. The polymer must not be classified as carcinogenic, mutagenic, or toxic to reproduction (CMR) by other international agencies;
  - b. The polymer must be either
    - i.a low concern polyester consisting only of monomers listed in Schedule 8 of the NSNR (Chemicals and Polymers); or
    - ii.a polymer that contains functional groups considered to be non- reactive in environmental and/or biological settings
  - Other information

Polymers

- **Experience To Date and Moving Forward**
  - Link to New Substances Program
    - expertise and assessment experience drawn from New Substances Program
    - 200-300 new polymers assessed per year in the New Substances Program, > 8000 total to date; so have extensive physical and chemical data, and toxicological data
    - have good knowledge of exposure streams for polymer industry and various sectors as well
  - Determination of Reduced Regulatory Requirements (RRR) polymer equivalency for CMP assessments:
    - assumed from onset that some polymers groupings could contain RRR polymers as defined under the *New Substances Notification Regulations*
    - specific technical data are needed for RRR determination (e.g., molecular weight, oligomers, monomers and percentages, structural info)
    - voluntary and S.71 polymer surveys produced useful data; a RRR determination was incorporated into rapid screening for polymers

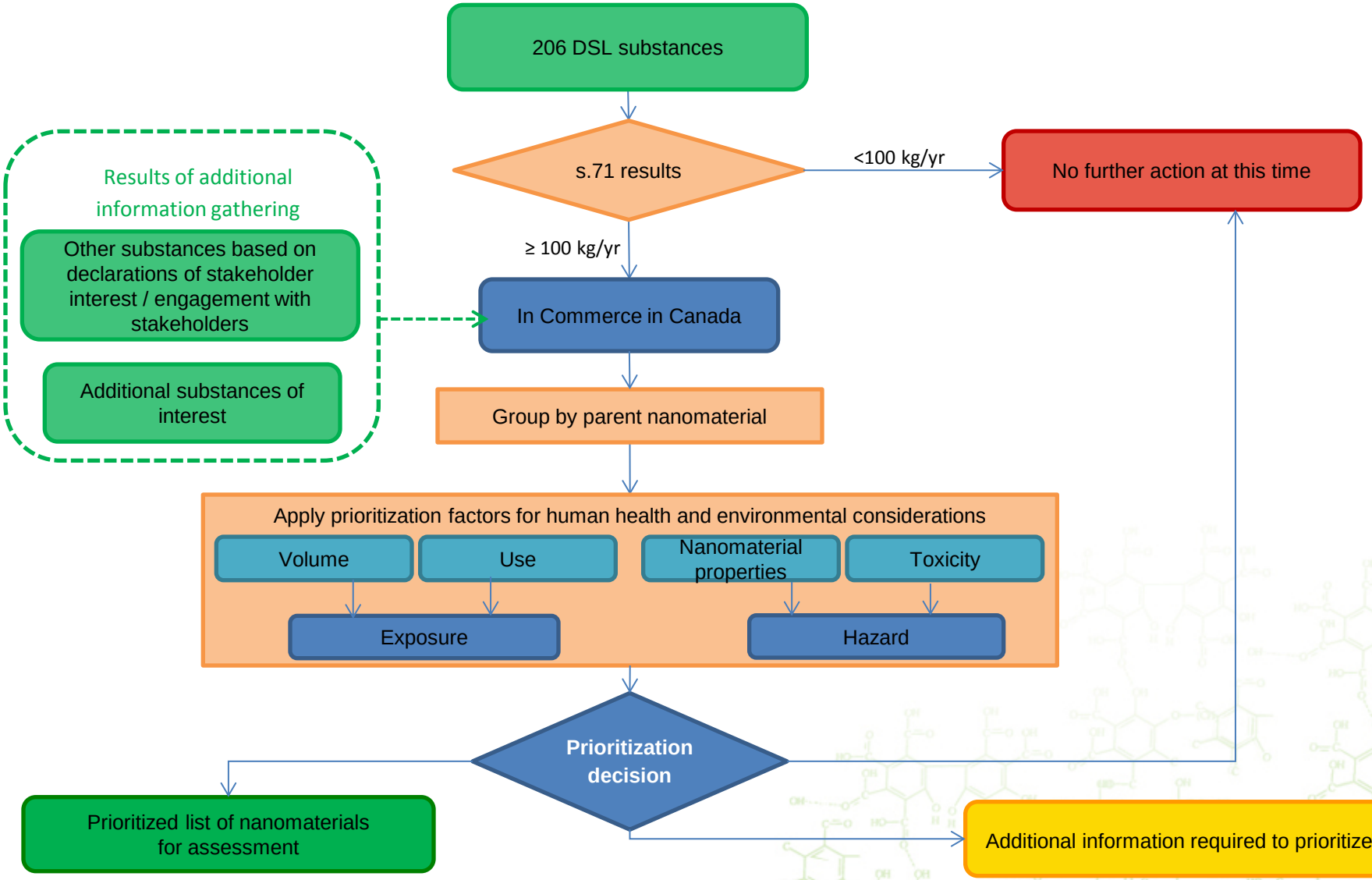
Nanomaterials

- Some substances with CAS numbers on the DSL also have a nanoscale form which may be in Canadian commerce (e.g., gold, silver, titanium dioxide) and have not been assessed under the existing substances framework

- Canada is developing a phased approach to address the legacy of nanomaterials that are already in commerce in Canada, as part of the CMP:
  - Establish a reference list of existing nanomaterials in Canada
  - Prioritize existing nanomaterials for action based on clear and transparent criteria
  - Take appropriate action on nanomaterials identified for further work

- **Experience To Date and Moving Forward**
  - A reference list of existing nanomaterials in Canada was established
  - Prioritization approach will be finalized, considering public comments (target January 2017)
  - Prioritization exercise will begin (target February 2017)

Proposed Prioritization Strategy for Nanomaterials



Metals/Metalloids: Moiety Assessment

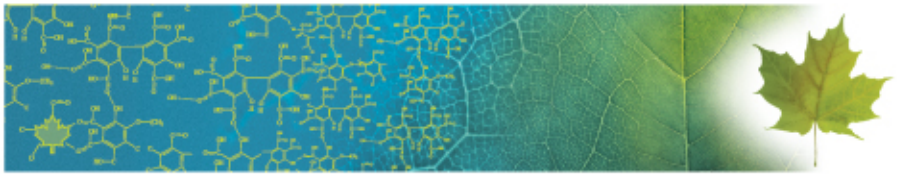
- Focusses on a discrete chemical entity of toxicological significance that is a common constituent of a group of substances
- All substances that contribute to the total loading of the inorganic moieties may be considered as part of these assessments

Experience To Date

- Examples of moiety assessments include: Cobalt and Cobalt-Containing Substances, Selenium and its Compounds, Boric Acid, its Salts and its Precursors
- Bioavailability and toxicity often vary with chemical speciation

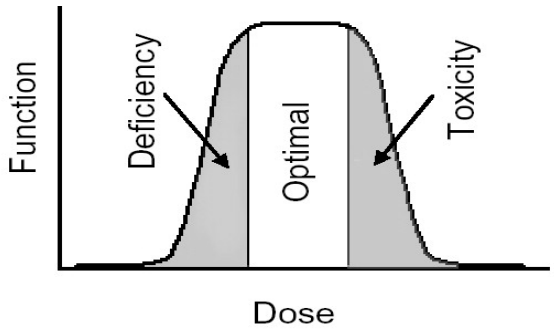
Moving Forward

- Moiety assessments are planned for several more groups of substances: Aluminum, Copper, Silver, Thallium, & Zinc



Metals/Metalloids: Essentiality

- A number of essential elements have been identified as priorities for assessment as a result of categorization (e.g., selenium, zinc)
- Certain essential nutrients for human health have a narrow optimal dose window (e.g., selenium)
- Assessments evaluate the potential for harm from elevated levels of exposures rather than deficiency or essentiality
  - Potential human health risks to certain populations that have or are likely to have elevated exposure levels
  - Regional background concentrations are factored into predictive modelling and are used to identify sites or areas with elevated environmental concentrations



UVCB Substances

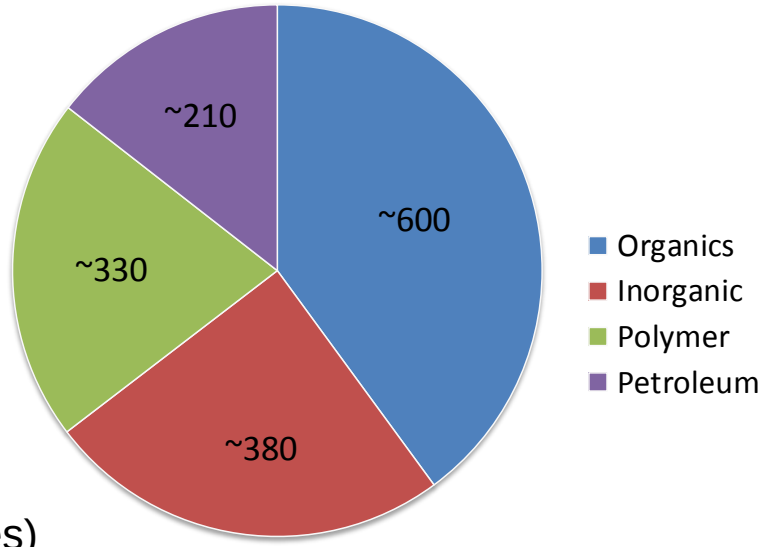
- The assessment of substances of Unknown or Variable composition, Complex reaction products or Biological materials (UVCBs) present a challenge as their chemical compositions are not well defined:
    - Within the same CAS RN, the constituent compounds can vary in number, identity and proportion
    - For some UVCBs (e.g., petroleum substances), composition can depend on factors such as operating conditions, feedstocks and processing units
- Representative structures may be selected to predict the overall behaviour of these substances and assess the potential hazard
- Whole mixture toxicological data, and/or concentration of high hazard constituents can be used to assess the potential hazard
- Toxicological data may be pooled across CAS RNs to construct toxicological profiles that are representative of a class

Canada's Chemicals Management Plan - Phase 3 (CMP3)

- Announced in May 2016
- Approximately 1500 substances left to be addressed before 2020
- Efficient "fit for purpose" approaches being further developed

CMP3 - Remaining Priorities

- Breakdown of chemical categories:
  - Organics (approximately 600 substances)
  - Inorganics (approximately 380 substances)
  - Polymers (approximately 330 substances)
  - Petroleum (approximately 210 substances)



- Functional use:
  - Most frequently reported uses in DSL IU2 were:
    - Paints and coatings (253 substances)
    - Personal care products (208 substances)
    - Cleaning and furnishing care (166 substances)
    - Lubricants and greases (158 substances)

- Combinations of function and chemical similarity are being explored

Fit-for-Purpose Approaches

- A fit-for-purpose approach ensures the ability to focus efforts on the substances of higher concern and to engage stakeholders on substances as efficiently as possible

- **Experience to Date and Moving Forward**
  - Throughout the CMP, a fit-for-purpose approach has been used (e.g., rapid screening of substances of lower concern, cumulative assessment)
  - The approaches taken may be different for the ecological assessment and the human health assessment
  - The Risk Assessment Toolbox was developed to formalize these approaches

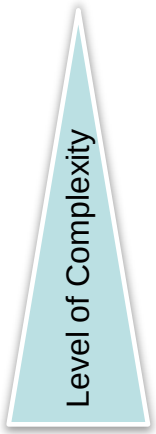
Risk Assessment Toolbox

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

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

Problem Formulation

- **ePROBLEM FORMULATION DATABASE (ePFDB)**
  - MS Access Database created internally
  - Contains information primarily on organic substances but also some inorganic and petroleum substances on the DSL and substances/substance groupings that are prioritized in CMP
  - Gives a ‘snapshot’ of the exposure potential and known hazard information to guide in selection of Approach Type and next steps in data gathering
    - from DSL and inventory updates, categorization and international assessments

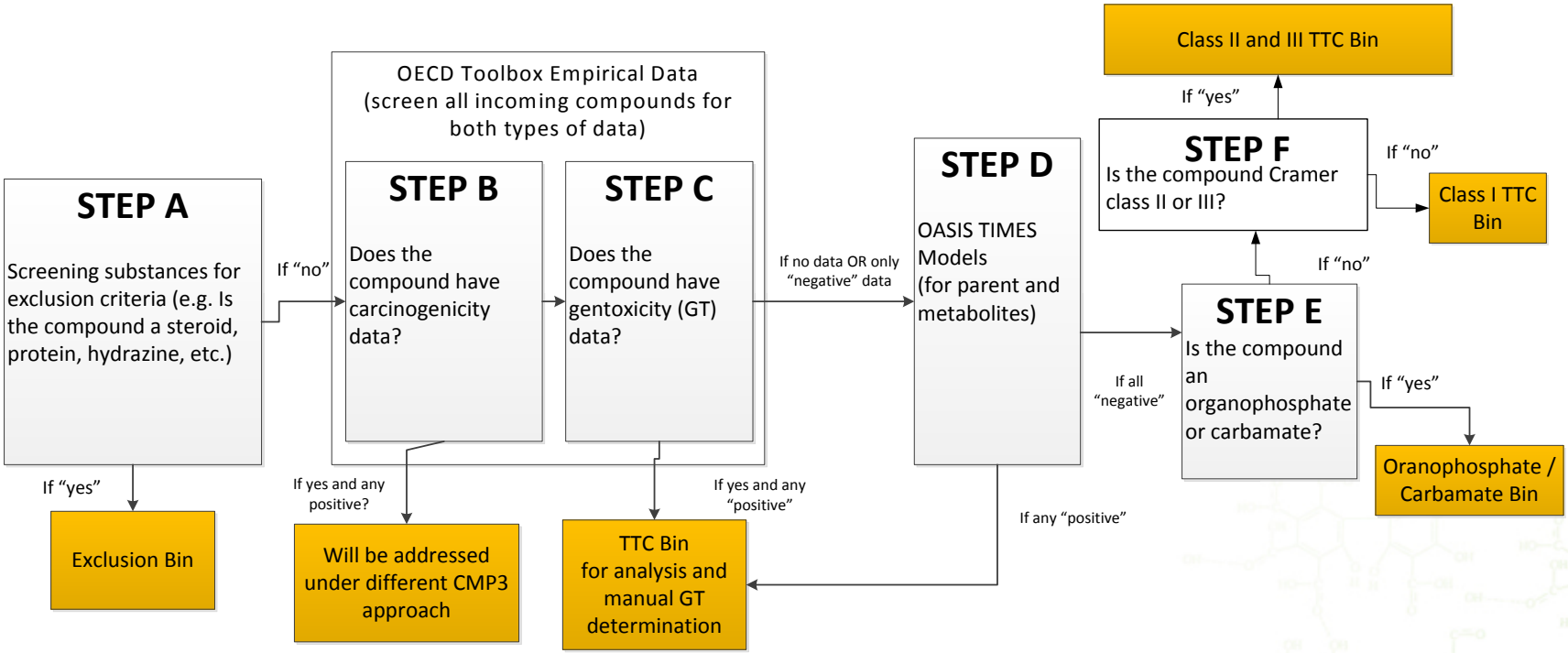
Threshold of Toxicological Concern (TTC) Approach

- 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



UVCB Substances

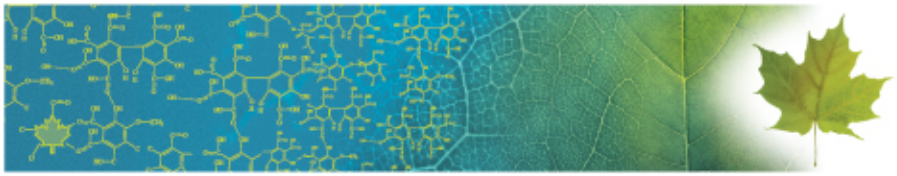
- UVCBs will continue to be addressed in CMP3
  - Petroleum substances
  - Inorganic UVCBs (e.g., sector-specific inorganic UVCBs screening assessment)
  - Organic UVCBs have been grouped with similar organics (e.g., hindered phenols, terpenes and terpenoids)

- Results of recent voluntary information gathering activities to collect composition and use information on CMP3 UVCBs will inform the risk assessments

Overall Assessment Approach

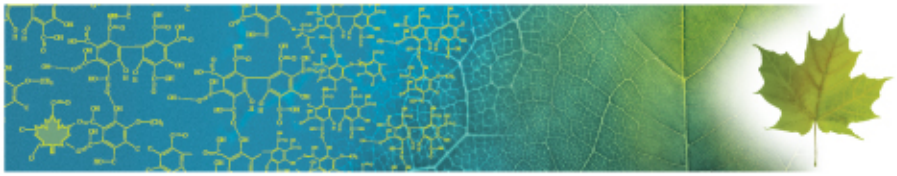
- Tiered approach:
  - Start with conservative assumptions and refine as necessary
  - Refinement may be limited by data availability

- Consider available data:
  - Use specific empirical information when available
  - Use chemical analogues for “read-across” purposes
  - Use computer models (“*in silico*” approaches)



Assessment Strategies: Multiple Approaches

- Individual substance assessments
  - “Traditional” approach, similar to Challenge screening assessments.
- Substance Groupings
  - Substance groupings were based on structural or functional similarities and assessment or management efficiencies, timing of international actions and stakeholder engagement.
- Moiety-based Assessments
  - Includes substances which may release moieties of potential concern.
  - Will consider all sources of the moiety to efficiently assess and effectively manage exposure and risk.
- Cumulative risk assessments
  - Where there is evidence to establish a common mode of action across substances, this approach will be considered.
- Biomonitoring
  - When adequate information on biomarkers and effects in humans is available
- Other



Risk Assessment Methodologies

- Consider or build upon international approaches or those used in other jurisdictions when developing methodologies for hazard, exposure or risk characterization
- Participate in OECD, WHO and other risk assessment methodology initiatives
- Maintain currency with advancing methodologies via participation in conferences and workshops
- Invest time in methodology aspects that support delivery of our program