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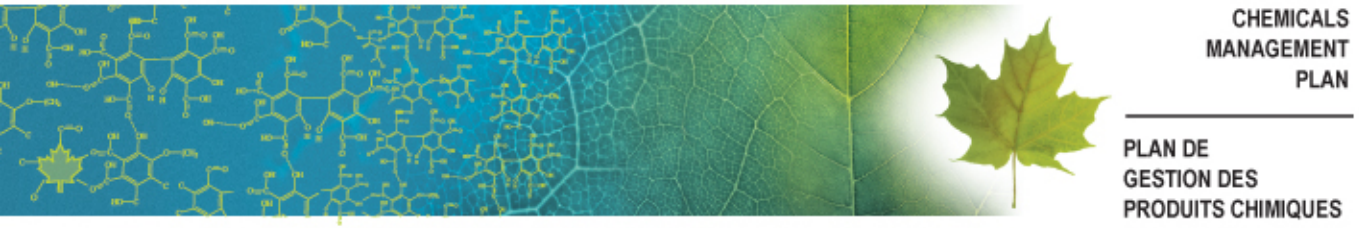
Hazard Characterization and Tools for Health Risk Assessment under CMP

Health Canada – PAHO Workshop

Lima, Peru

November 8-10, 2016



Canada

Outline

- Information Gathering
- Data Analysis
- Critical Effects
- Critical Effect Levels/Point(s) of Departure
- Use of New Approach Methodologies

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

Information Gathering

- Identify other appropriate international/national assessments
  - World Health Organization, International Programme on Chemical Safety
  - International Agency for Research on Cancer
  - Organization for Economic Cooperation and Development
  - US Environmental Protection Agency
  - Other Program Areas within Health Canada (e.g., Pest Management Regulatory Agency)
  - Others

Determine Approach Type

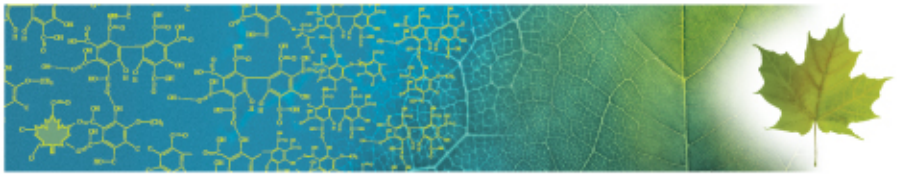
- Key is to be efficient, tailor effort to assess
- If existing acceptable assessment identified, consider Type 3-1 approach
  - Generally, conclusions of assessment accepted
  - Using comprehensive search strategy for consistency, search literature for one year prior to publication of assessment
  - Determine if new information would alter earlier conclusion
  - If not, rely heavily on other assessment outcome; minimize effort required to assess
  - If new data impact earlier conclusion, focus attention principally on that area or new area of concern

Determine Approach Type

- If no existing acceptable assessment identified, select Type 3-2 (de novo assessment) or Type 3-3 (more complex de novo assessment)
  - Using comprehensive search strategy for consistency, search literature for any relevant information from human epidemiological studies, toxicological studies in experimental animals and relevant in vitro studies (e.g., genotoxicity)
  - If needed to fill critical data gaps and time permits, initiate focussed research

Analysis of Hazard Information

- Informed by exposure potential
  - Consider relevant durations and routes of exposure
    - Duration: Long term and/or shorter term effects data important, depending on likely sources of exposure (i.e., exposure via environmental media & food vs. short term exposure from use of consumer products)
    - Route: ideally, hazard studies conducted by relevant routes of exposure
- Consider the potential for toxicity to humans of the chemical
  - Physical & chemical properties
  - Toxicokinetics – how much the body absorbs, distributes, metabolizes and eliminates the chemical (not always necessary to delve too deeply for screening level assessment)



Analysis of Hazard Information

- Summarize/tabulate studies:
  - Epidemiological data – greater weight given to analytical studies (cohort and case-control studies)
- Organize non-human effects data by duration and focus of study; for example:
  - Acute toxicity
  - Short term toxicity
  - Subchronic toxicity
  - Chronic toxicity/carcinogenicity
  - Genotoxicity
  - Reproductive toxicity
  - Developmental toxicity
  - Other targeted studies (e.g., immunotoxicity)
- Within each duration type, organize by species and route of exposure (e.g., oral, inhalation, dermal, depending on expected routes of exposure)

Analysis of Hazard Information

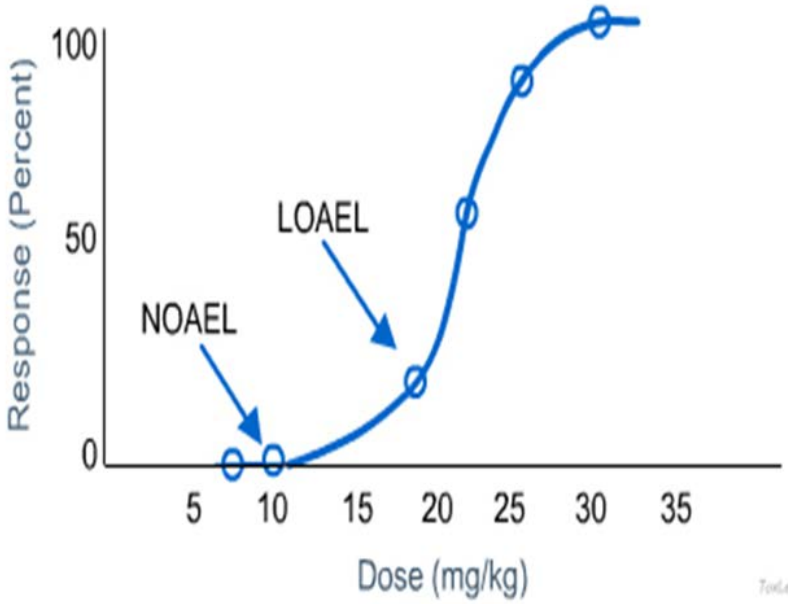
- Look for patterns in effects data – weight and strength of evidence
  - Nature of effects, target organs/systems reported in multiple studies, in multiple species
  - Did incidence/prevalence or severity of response increase with increasing dose/concentration? (examine dose-response)
  - What effects 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
- Author reported conclusions generally accepted
- Consider evidence for human relevance of observed effect, taking into consideration existing knowledge *in a screening context*
- If substance exposure sources are both long term and short term, and/or via multiple routes, select critical effects from appropriate studies to estimate risk from range of sources, for example:
  - if food is key source, select longer term oral study if available
  - if product involving dermal contact used occasionally, short term dermal study ideal

Determination of Critical Effect Levels

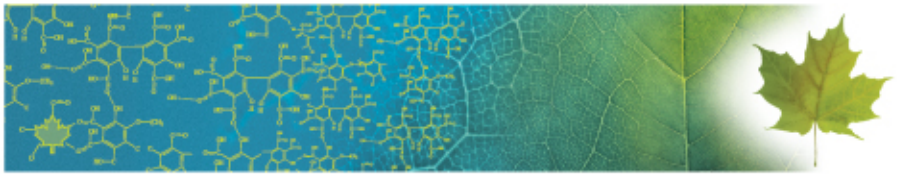
- Consider multiple endpoints across the entire database to establish critical effects and critical effect levels/Points of Departure (NO(A)ELs, LO(A)ELs, BMDs)
  - What dose causes an adverse effect on endpoint of concern?
  - Author reported effect levels generally accepted



Obtained from:
toxlearn.nlm.nih.gov

Substances With Little Or No Data

- Use of New Approach Methodologies (NAM)
  - different data gap filling methods/approaches
  - Ideally together
- (Q)SAR models (e.g., Leadscope, DEREK)
- Analogue/Category Read-across (e.g., OECD QSAR Toolbox)
- In vitro High Throughput Screening (e.g., ToxCast, Tox21)
  - HTS assays are automated methods that allow for a large number of chemicals to be rapidly evaluated for a specific type of bioactivity at the molecular or cellular level
- Toxicogenomics
  - The study gene and protein activity within particular cell or tissue of an organism in response to toxic substances (high content)
- Validation of alternative approaches/models critical to understand uncertainty associated with these methods



Predictive Tools for Hazard Assessment

Commercial

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

Non-commercial

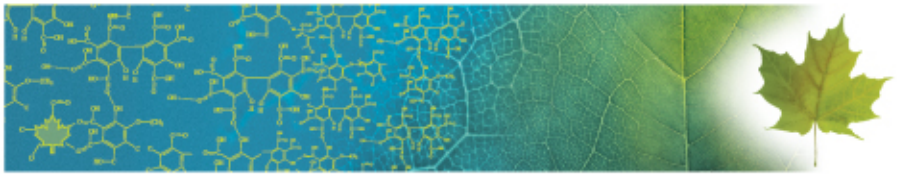
- *OECD QSAR Toolbox*
- *Toxtree*
- *OncoLogic*
- *VEGA Caesar*
- *Analog Identification Methodology (AIM)*

Cheminformatics tools

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

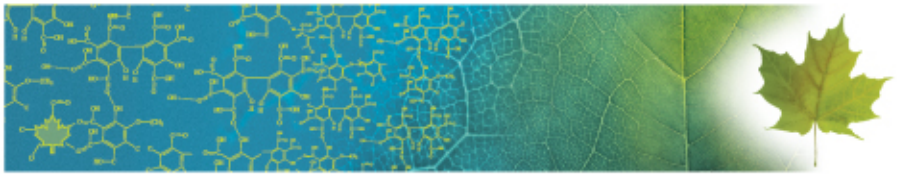
OECD QSAR Toolbox

- Freely available tool to fill missing toxicological data on substances by read across approach (https://www.qsartoolbox.org/)
- Read across could be carried out either by building chemical category or using an analogue
- Contains mechanism-based structure fragments (profilers)
- Has built-in simulators of mammalian metabolism
- Creates reports in different formats



OECD QSAR Toolbox

- Hosts several toxicological databases, ADME information, chemical inventories and facilitates data searching
- Currently has one Adverse Outcome Pathway (AOP) for skin sensitization…..more to come in future
- Hosts several models to predict a variety of physical, chemical properties of chemicals
- Computes a variety of structural similarity indices
- Contains a large amount of background data on reaction mechanisms



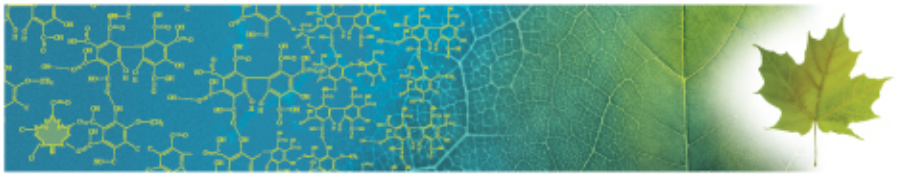
Read Across Process

	Chemical 1	Chemical 2	Chemical 3	Chemical 4	
Structure	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	
Property 1	● →	○	● →	○	SAR/Read-across
Property 2	● →	○	○ ←	●	Interpolation
Property 3	○ ←	●	● →	○	Extrapolation
Activity 1	● →	○	● →	○	SAR/Read-across
Activity 2	● →	○	○ ←	●	Interpolation
Activity 3	○ ←	●	● →	○	Extrapolation

● Existing data point ○ Missing data point

Database Uncertainties and Confidence

- Characterize uncertainties in database as a whole as well as for key studies
  - Not just data gaps, but also impact on decision making
  - Consistency of database, repeated evidence of critical effects and support around critical effect levels
  - Likelihood that effects observed in laboratory animals relevant to humans
- Statement on confidence in database
  - Greater confidence in consistent empirical data; lesser confidence when relying on alternative sources of information
- Identify what information would reduce uncertainty/increase confidence
- Uncertainties & confidence factor into risk characterization



Annex

DMOB* read-across example

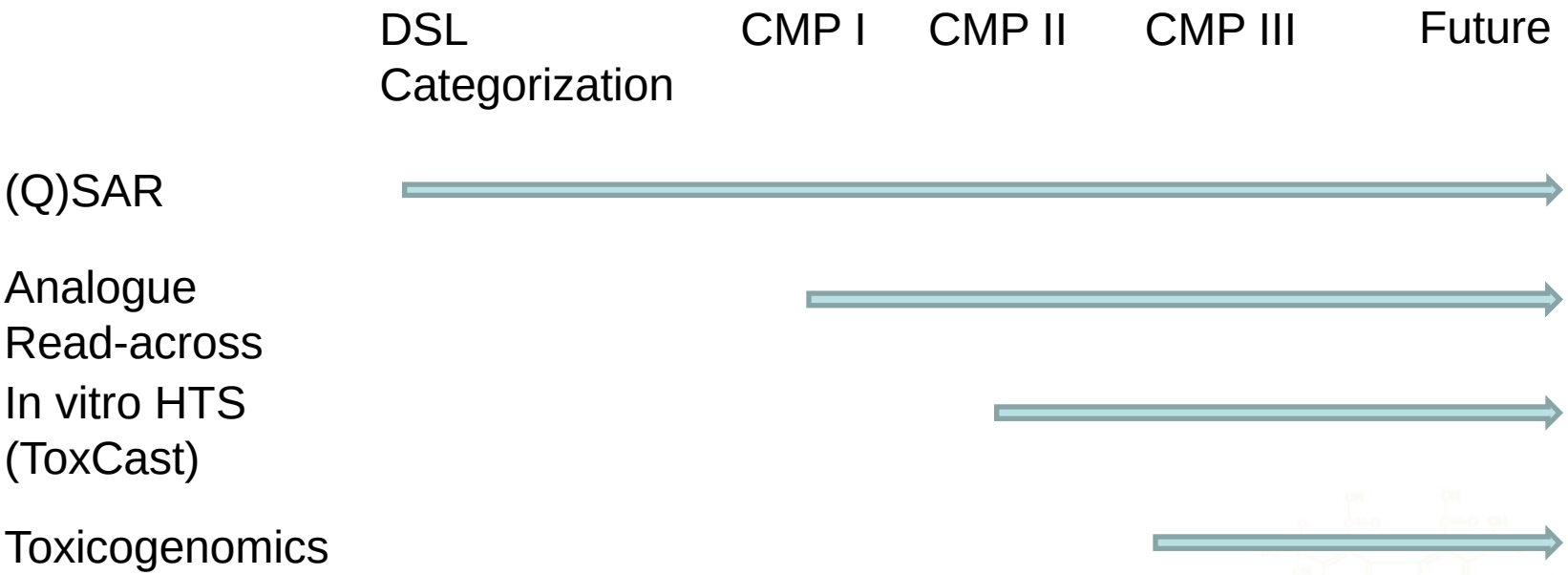
	Supporting Common Metabolite	Member 1	Member 2	Member 3	Member 4	Member 5	Member 6	Member 7	Member 8	Member 9	Member 10	Member 11	Member 12	Member 13
CAS	119-90-4	2429-71-2	2429-74-5	6449-35-0	67923-89-1	70210-28-5	71550-22-6	75659-72-2	75659-73-3	75673-18-6	75673-19-7	75673-34-6	75673-35-7	75752-17-9
Summary of data gap filling														
Experimental result (non-GLP)	Positive S. typhimurium (TA 98; TA 100; TA 1538) with S9 (rat)	Positive S. typhimurium (TA 1538) with S9 (hamster) + FMN	Positive S. typhimurium (TA 98) with S9 (hamster) + FMN modified according to Prival et al.	Positive S. typhimurium (TA 98) with S9 (hamster) + FMN		Positive S. typhimurium (TA 98 / TA 100) with S9 (hamster) + FMN								
Integrated conclusion (eg. read-across)					**Read Across overall trend of category** Positive S.typhimurium (TA 98, 100, 1538) with reductive modifications and metabolic activation		**Read Across overall trend of category** Positive S.typhimurium (TA 98, 100, 1538) with reductive modifications and metabolic activation	**Read Across overall trend of category** Positive S.typhimurium (TA 98, 100, 1538) with reductive modifications and metabolic activation	**Read Across overall trend of category** Positive S.typhimurium (TA 98, 100, 1538) with reductive modifications and metabolic activation	**Read Across overall trend of category** Positive S.typhimurium (TA 98, 100, 1538) with reductive modifications and metabolic activation	**Read Across overall trend of category** Positive S.typhimurium (TA 98, 100, 1538) with reductive modifications and metabolic activation	**Read Across** Positive S.typhimurium (TA 98, 100, 1538) with reductive modifications and metabolic activation	**Read Across** Positive S.typhimurium (TA 98, 100, 1538) with reductive modifications and metabolic activation	**Read Across overall trend of category** Positive S.typhimurium (TA 98, 100, 1538) with reductive modifications and metabolic activation

*3,3' Dimethoxybenzidine based direct dyes

Historical use of (Q)SAR applications

late 1990	Pilot phase screening level assessments	Commercial (Q)SAR models; support weak datasets and analogues
2000-06	DSL Categorization	Commercial (Q)SAR models; basis for decision making (prioritization)
2006-11	Ministerial Challenge Phase CMP (high priorities)	Commercial and some public domain (Q)SAR models, Metabolism, Analogue identification, Read-across; basis for decision making but mainly supportive evidence
2011-	CMP II (data poor substances)	Commercial and public domain (Q)SAR models, Analogue identification, Read-across, Metabolism, Chemical categories, in-house models/tools

Progression in Use of Alternate Technology in Chemical Hazard Assessment



New Approach Methodologies

International Collaborations & Contributions

Exploring utility of HTS data in regulatory applications under the CMP

caleidos

QSAR model validation
CMP chemical space

Genomics Committee
Non-animal methods project

IUCLID 5
INTERNATIONAL UNIFORM CHEMICAL INFORMATION DATABASE

OECD
BETTER POLICIES FOR BETTER LIVES

- Adverse Outcome Pathways (AOPs)
- Integrated Approaches to Testing and Assessment (IATA)
- QSAR Toolbox Management Group