New Approaches in Hazard Identification:

The Role of QSARs in the Categorization of Canada's Domestic Substances List (DSL)

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Overview

- Categorization of Canada's Domestic Substances List
  - Setting priorities and identifying emerging chemicals of concern
  - Categorization criteria for Environment and Health Canada
- Challenges during categorization
  - Paucity of experimental data- forced heavy reliance on QSARs/models
  - The role of QSARs in identifying hazards and setting priorities
- Moving forward after Categorization
  - Canada's Chemical Management Plan (CMP)
  - QSARs, and "The Challenge" to industry
- Current and Future actions

Categorization Program - Identification of Chemicals of Emerging Concern

- Mandated under *Canadian Environmental Protection Act,1999* (CEPA 1999)
- Categorization was a 7 year prioritization process that involved the systematic identification of substances on the DSL ("existing substances") that should be subject to screening assessment
- Original DSL approx 23 000 substances
- Triage exercise to set priorities for further action
- Prior to this, the evaluation of existing substances was limited to risk assessments for specified numbers of Priority List Substances (5 yr timeframe)

What was the Objective of Categorization?

- Identify substances, based on available information that:
  - May present, to individuals in Canada, the greatest potential for exposure; or
  - Are persistent (P) **or** bioaccumulative (B), in accordance with the Persistence and Bioaccumulation regs, **and** inherently toxic (iT) to humans or to non-human organisms, as determined by lab or other studies

Ecological Categorization Criteria for P, B, and non-human iT

Persistence

A substance is considered persistent if its transformation half-life satisfies the criterion in any one environmental medium or if it is subject to long-range transport

Medium	Half-life
Air	≥ 2 days (or LRT)
Water	≥ 6 months
Sediment	≥ 1 year
Soil	≥ 6 months

Bioaccumulation

BAF >= 5000

or

BCF >= 5000

Or

LOG Kow >=5

iT –non-humans

Acute aquatic toxicity of $LC(EC)_{50} \leq$ 1mg/L, or a chronic aquatic toxicity of NOEC ≤ 0.1 mg/L

Categorization Criteria for Human Exposure and Human iT

Greatest Potential for Exposure

- **Simple Exposure Tool (SimET)**

  Relative ranking of all DSL substances based on number of submitters, quantity in commerce and sum of expert ranked use codes. Ranking separated into one of three groups

  1) Greatest Potential for Exposure (GPE)
  2) Intermediate Potential for Exposure (IPE)
  3) Lowest Potential for Exposure (LPE)

Inherent toxicity to humans (iT)

- **Simple Hazard Tool (SimHaz)**

  Identification of high or low hazard compounds by various international agencies based in a weight of evidence of multiple endpoints

High Hazard Substances - Health

Simple Hazard (SimHaz) Tool:

1. Listed as Carcinogenic
   - Health Canada Drinking Water Guidelines 1995
   - US EPA 1986 Cancer Guidelines
   - US EPA 1999 Proposed Cancer Guidelines
   - US NTP Report on Carcinogens 2002
   - IARC 2000
   - EU (EINECS 2004)
2. Listed as Genotoxic, EU (EINECS 2004)
3. Listed as Repro/Devo Tox, EU (EINECS 2004)

QSAR Use by Health Canada

- While QSARS not used as part of the SimHaz tool, they were utilized as part of Health Canada's Complex Hazard tool (ComHaz)
- ComHaz looked at substances that were found by Environment Canada to be P and/or B and not eco iT and that were found to be IPE based on the Simple exposure tool
- ComHaz is a hierarchy of toxicological endpoints which considers both empirical and modelled data
- QSAR models considered within ComHaz include TOPKAT, CaseTox, and DEREK

Information Sources used to identify hazards for Ecological Categorization

- Publicly available databases, journals, internet, international lists and data sources
- Voluntary data submitted by Industry
  - involved submission of unpublished studies/ not publicly available
  - EC made requests for studies from companies as well (e.g. request original study supporting values cited in an MSDS)
  - Industry submissions of category approaches, with justifications and supporting data
- Generated some phys-chem data (e.g. water solubility) and ecotoxicity data (e.g. toxicity of 63 metals to *Hyallella azteca*)
- Modelled data - QSARs
- Grouping exercises, in particular for UVCBs, to utilize analogous/read-across experimental and model data.

Ecological Categorization- Challenges along the way

- Diversity of substances (required different approaches for categorization)
  - Discrete organics 50%; Inorganics 10%; Polymers 20%; Unknown, Variable in composition, Complex reaction products, and Biologicals (UVCBs) 20%
- Availability of experimental data
  - For example, for more than 11,315 organic substances examined,
    - Experimental aquatic toxicity data was found for 1200 substances (80% accepted)
    - Experimental P data was found for 1500 substances (50% accepted)
    - Experimental B data was found for 440 substances (80% accepted)
- As a result, other sources of data/information, like QSARs, were required to complete categorization within the legislated time frame

Heavy Reliance on QSARs & Models

- QSARs used to generate P, B and IT values, as well as for the estimation of Phys-chem values
- Where “representative structures” could be developed for the UVCBs, QSARs were also used extensively for these substances
  - QSAR results were used as part of the grouping exercises which formed a major component of the UVCB categorization approach
  - QSAR results used in some cases to refine some groupings (i.e. predictions used along with expert judgement)

Role of QSARs in Hazard identification and Priority Setting

- Experimental data was preferred over modelled
- However, as an example, because of the paucity of experimental data for the 11,315 Discrete organics on the DSL
  - 86% (9705) substances required QSARs for categorization of P
  - 85% (9639) substances required QSARs for categorization of B
  - 80% (9071) substances required QSARs for categorization of iT

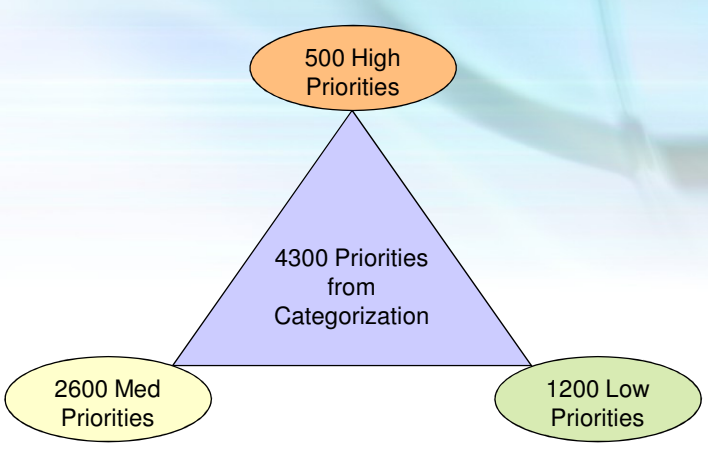
AND

- 68% (7734) of 11315 organics required QSAR model estimations for determination of all 3 ecological categorization endpoints (PBiT)
- Conversely, only ~5-6% (632) of 11315 categorizations decisions did not require QSARs for at least one of the 3 ecological endpoints
  - Decisions made with experimental data, category approaches or a combination of the two

Results of Categorization brings a challenge: how to distinguish "Priorities among Priorities"

- Health Canada & Environment Canada identified 4300 substances requiring further work/action
- Needed to develop an approach to identify priorities amongst larger set of priorities
- Considerations for the first round of priority setting and upcoming actions :
  - The degree of hazard/risk (e.g. PBiTs a top priority)
  - Commercial activity in Canada
  - Existing/ongoing risk assessment and risk management activities
  - Opportunities to engage internationally and "share the work" for a global issue

From 23,000 to 4300 Substances



Top 500 Priorities

- In December 2006, Government announced a Chemicals Management Plan (CMP)
  - plan to address chemicals that are harmful to human health or the environment
- Within the CMP, the top 500 priorities (identified through categorization) are addressed through 4 components:
  - Challenge Program for substances believed to be in commerce – ~200 substances
  - Significant New Activity (SNAcs) for substances believed to not be in commerce
  - Petroleum Sector Stream – a focused sectoral approach
  - Substances that are already in the assessment or management stream

Why Canada is using a Challenge initiative to deal with the ~200 priorities for action?

- Challenge to industry to provide information that:
  - Improves, where possible, information for risk assessment
  - Identifies industrial best practices in order to set benchmarks for risk management and product stewardship; and
  - Collects environmental release, exposure, substance and/or product use information
- The absence of information will not preclude the gov't from taking action that safeguards human health and the environment- Precautionary approach/principle
- QSARs played a large role in identifying the priorities for action in the Challenge, and may in cases form the basis for subsequent government action

QSARs & the Challenge Substances

- Approximately 75% of PBiTs on the Challenge are there as a result, in whole or in part, of QSAR predictions
  - 50% (64 of 128) PBiTs in challenge are PBiT QSAR
- As part of the challenge, the data (both QSAR and experimental) for which the categorization decisions were based is presented in so-called Substance Profile
- The purpose of these substance profiles are to show stakeholders what we know about the substance.
- The key objective in developing and providing these are to identify opportunities to submit information to support the activities taking place under the Chemicals Management Plan.

Current & Future Actions

- Continue release of Substance Profiles
  - being released in a 12 batches of 15-20 chemicals every 3 months over 3 years
  - Batch 3 profiles released publicly in August
- Continue to investigate potential uses for QSARs to further refine priorities (e.g. the 2600 medium priorities)
  - Consideration for cross-sectional diameter
  - Metabolism (e.g. Catabol)
  - Use of metabolic data to improve bioaccumulation predictions
  - Use of tools such as Leadscope/OECD Tool box for grouping and utilization of analog/read-across data
    - Take advantage of what experimental data we do have

Contact Information

- **Chemical Substances Web Site:**
  - http://www.chemicalsubstances.gc.ca
  - **Challenge documentation**
    - http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/index_e.html

Contact for Inquiries or Submissions:

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- **CD ROMS with results of categorization available upon request**