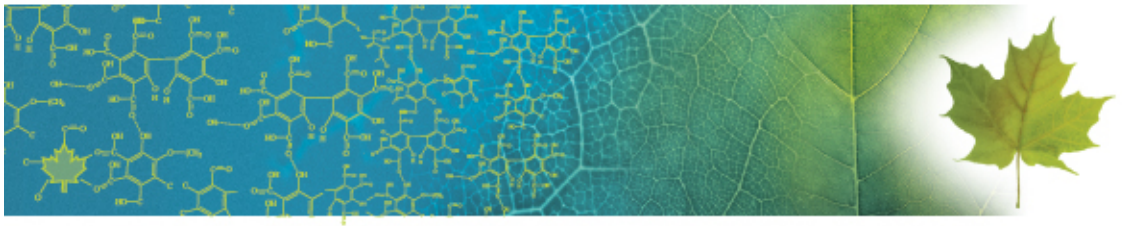
Government of Canada | Gouvernement du Canada

Canada's Categorization of Existing Substances under CEPA 1999

Health Canada – PAHO Workshop

Lima, Peru

November 8-10, 2016



CHEMICALS MANAGEMENT PLAN

PLAN DE GESTION DES PRODUITS CHIMIQUES

Canada

Outline

- Regulatory Background for existing chemicals
  - The *Canadian Environmental Protection Act, 1999*
- Categorization
  - Criteria, tools, approaches
  - Results
- The Way Forward

Canadian Environmental Protection Act (CEPA)

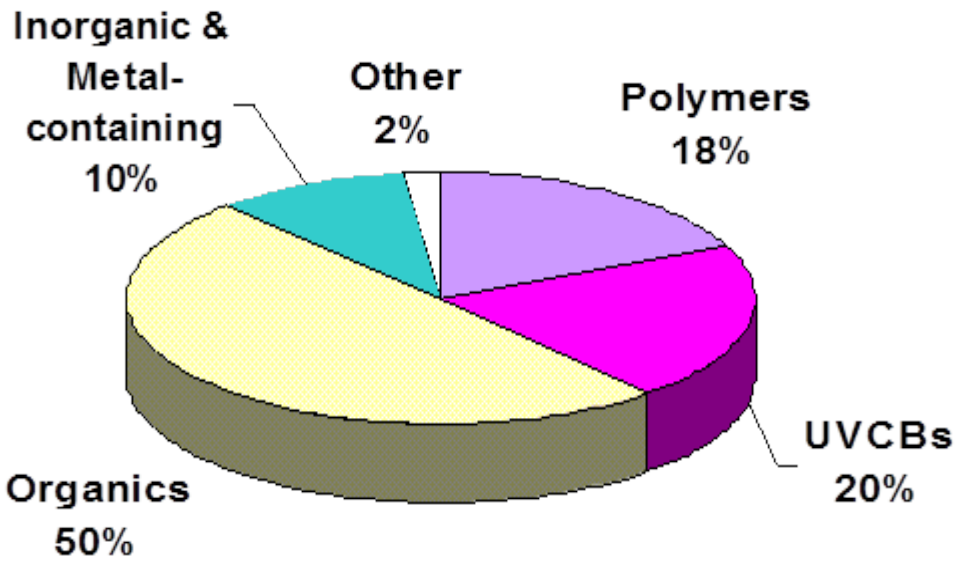
- First promulgated in 1988; renewed in 1999
- Ministers of the Environment and Health mandated to assess and manage risks to environment and human health of new and existing substances
- The Domestic Substances List (DSL) was created in 1991 for the purpose of defining a “new substance” under CEPA
  - Any chemical, polymer, nanomaterial or product of biotechnology not listed on the DSL is considered to be new to Canada and is subject to the notification requirements under New Substances Notification Regulations
- Approximately 23,000 substances (industrial chemicals) on the DSL
- Substances are regularly added to the DSL through the new substances program

Creation of the DSL

- A list of substances that are “in commerce” in Canada (i.e., “existing substances”)
- Substances nominated as being, between 1984-1986:
  - In Canadian commerce or used for commercial manufacturing in Canada, or;
  - Manufactured or imported in Canada at >100 kg/year
  - Does not include: contaminants, by-products and wastes
- Type of information originally collected on DSL substances in 1987 included:
  - Company Headquarters and Site of Manufacture
  - Type of Commercial Activity (import or manufacture)
  - Use Code
  - Quantity Range
  - Substance CAS # and Name
  - Molecular Formula/Structural Info (if available)

Types of Substances on the DSL

(total 23,000 substances)



***UVCB** = **U**nknown or **V**ariable composition, **C**omplex reaction products or **B**iological material

Obligations under CEPA for Substances

- Ministers required to determine if substance is “toxic” as defined in the Act; i.e., if it is entering or may enter the environment in quantities that may:
  - Have an immediate or long-term harmful effect on the environment,
  - Constitute a danger to the environment upon which human life depends, or
  - Constitute a danger to human health or life

- Substances determined to be “CEPA toxic” require risk management

Addressing Existing Substances under CEPA

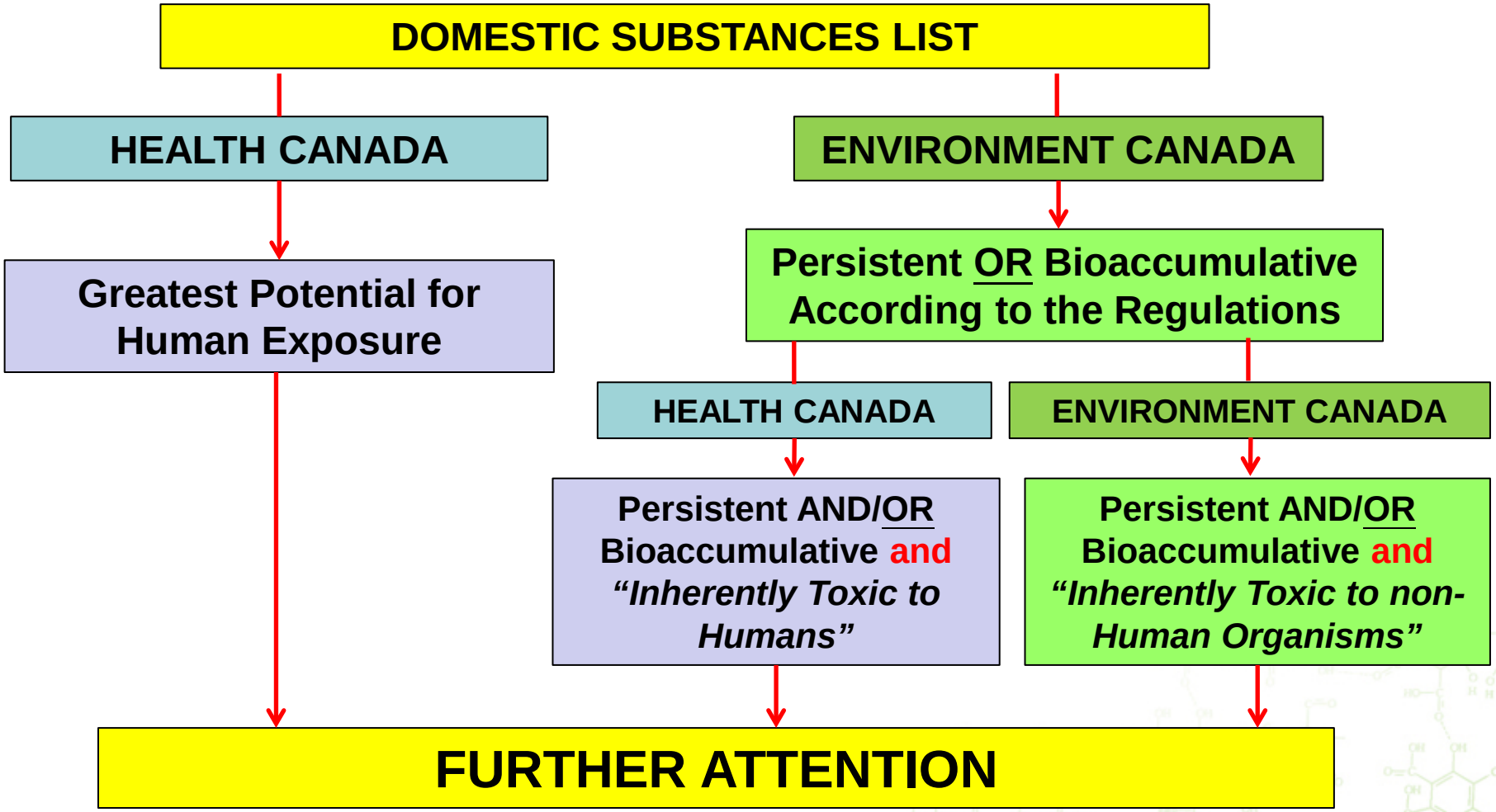
- CEPA 1988
  - Focus on pollution management
  - Priority Substance List (PSL) assessments
    - In-depth, complex; 5 year legislated deadlines
    - PSL1 (n=44 substances, released in 1989)
    - PSL2 (n=25 substances, released in 1995)

- CEPA 1999
  - Focus on pollution prevention
  - Ministers' mandate expanded
  - Categorization of entire DSL (n = 23,000)
  - Screening assessments for categorized substances
  - Priority Substances List assessments

Categorization

- CEPA 1999 required Ministers of the Environment and Health to (by September 14, 2006) categorize the 23,000 substances on the DSL according to specific criteria to identify substances that:
  - May present, to individuals in Canada, the **greatest potential for exposure**; **or**
  - Are **persistent** (P) **or bioaccumulative** (B), in accordance with the regulations, **and inherently toxic to humans or to non-human organisms**, as determined by laboratory or other studies
- Categorization was a prioritization process that involved the systematic identification of substances that should be subject to a screening assessment
- There are new substances added to the DSL but these have already undergone assessment and therefore not subject to the categorization process.

Categorization Process



Categorization Challenges

- No precedent, leading development of methodology
- Legislated deadline (7 years)
- Large number of substances with limited or no empirical data
- Varied types of substances on DSL
- Need to develop protective, transparent, scientifically credible approaches and criteria to identify priorities for environment and/or human health
- CEPA 1999 did not address how to further prioritize after categorization

Meeting the Mandate - Process

- Key: Development of robust proposals for review in public forum, including:
  - Peer input and peer review of various components by experts internationally
    - including those from stakeholder groups selected by 3rd party
  - Workshops of stakeholders to solicit input on specialized aspects
    - Interpreting use codes
- Interfaced internationally to access forward looking peer reviewed methodology addressing critical areas (in particular predictive tools) from all sectors
  - Where industrial stakeholders particularly were encouraged to contribute
- Continued updates to broad range of stakeholders; combined format preferred
- Communications pieces prepared & distributed as soon as various components conceptualized

Categorization Criteria/Tools

- Environment Canada
  - Persistence
  - Bioaccumulation
  - Inherent toxicity to non-human organisms

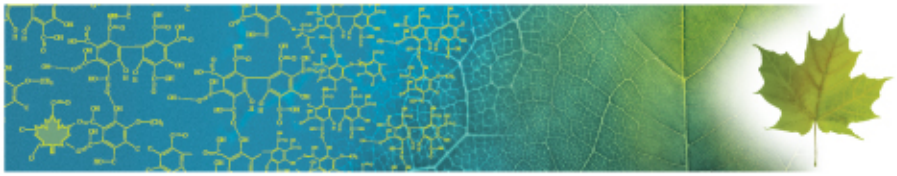
- Health Canada
  - Potential for Exposure
    - Simple tool
  - Inherent toxicity to humans
    - Simple & Complex tools

Challenges For Ecological Categorization

- Availability of empirical data
  - For example, for more than 11,500 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)

Information Sources

- Publicly available databases, journals, internet, international lists and data sources
- Voluntary data submitted by Industry
- Generated some phys-chem data and ecotoxicity data
- Modelled data - QSARs (Quantitative Structure Activity Relationships)
- Use of “read-across” data (from analogs)/apply grouping (category) approach



Data Preference for P B iT Profiles

Preference	P	B	**iT**
Higher	Experimental		
Medium	Analogue / Groupings / Scientific rationale		
Lower	Modelled (QSAR)		

Technical Approaches/Strategic Guidance

Organics

- DSL Technical Advisory Working Group (1999-2001)
- October 2002 Technical Workshop
- Guidance Manual for the Ecological Categorization of Organic and Inorganic Substances on the DSL (2003)

Inorganics

- Inorganics Working Group (IWG) (2000-2001)
- Findings and Recommendations from the IWG Report (2001)
- Guidance Manual for the Ecological Categorization of Organic and Inorganic Substances on the DSL (2003)

UVCBs

- Golder Associates' Report on Developing an Approach for UVCBs (2003)
- Boreal Associates' Report on Developing an Approach for UVCBs (2004)
- Approach Document for Ecological Categorization of UVCBs (2005)
- Category Approaches Documents (2005)

Polymers

- Approach Document for Ecological Categorization of Polymers (2005)
- Category Approaches Documents (2005)

Organometallics

- Approach Document for Ecological Categorization of Organometallics (2005)

Categorization Criteria for P, B, and Non-Human iT

Persistence (P)

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
Water	≥ 6 months
Sediment	≥ 1 year
Soil	≥ 6 months
(or LRT)	

Bioaccumulation (B)

BAF ≥ 5000 or
BCF ≥ 5000 or
log Kow ≥ 5

Inherent toxicity (iT) – non-humans

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

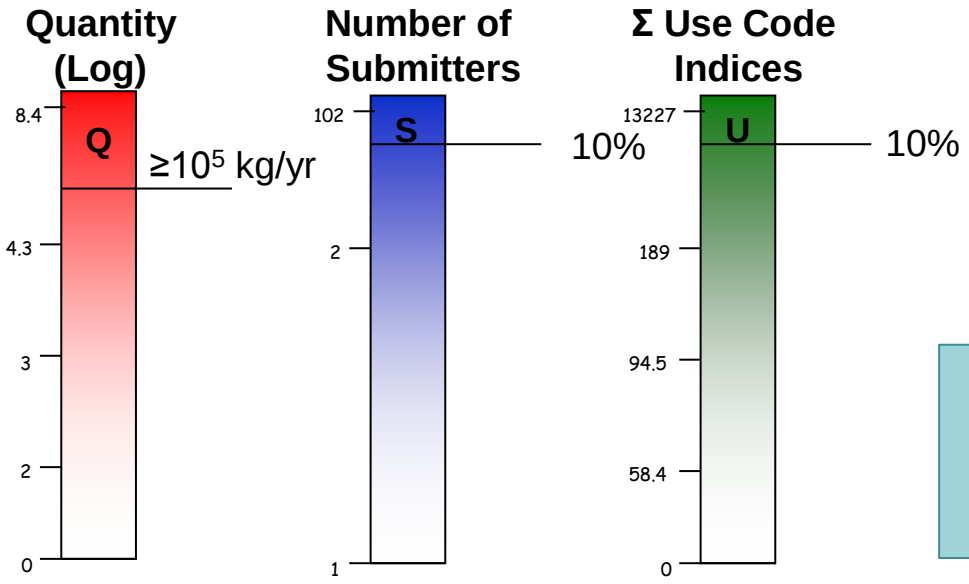
Categorization: Human Health Challenges

- Early recognition that legislative construct for categorization would not identify all priorities from human health perspective
- Persistence and Bioaccumulation not key determinants of potential to harm human health for all types of substances
- Other properties more relevant for some chemicals (e.g., reactive compounds)
    - P or B ≠ human exposure
    - P or B ≠ highest priorities for human health hazard
- Simple and complex tools developed to identify health priorities

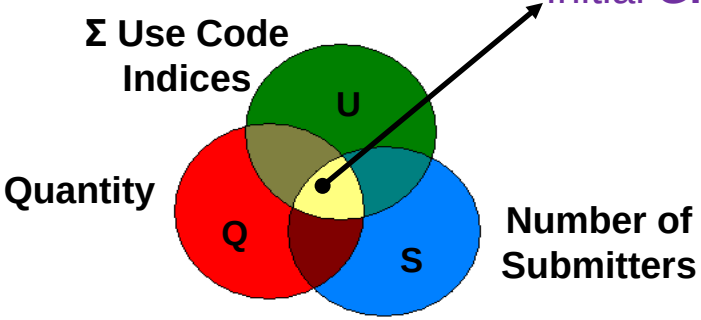
The Simple Exposure Tool - SimET

- SimET was a relative ranking tool by which all substances on the Domestic Substances List were “binned”
- Maximal use of the limited, comparable data for all 23,000 DSL compounds
  - Prevented bias to data-rich compounds
- Based on three different lines of evidence:
  - quantity (estimated annual quantity of use, **Q**),
  - number of submitters (**S**)
  - use (sum of normalized expert ranked use codes, **U**, reflecting two workshops)
- Limited expert judgement

Simple Exposure Tool (SimET)



Relative Ranking for all DSL substances



Initial **GPE** list of 849 substances

Criteria for Greatest, Intermediate & Lowest Potential for Exposure

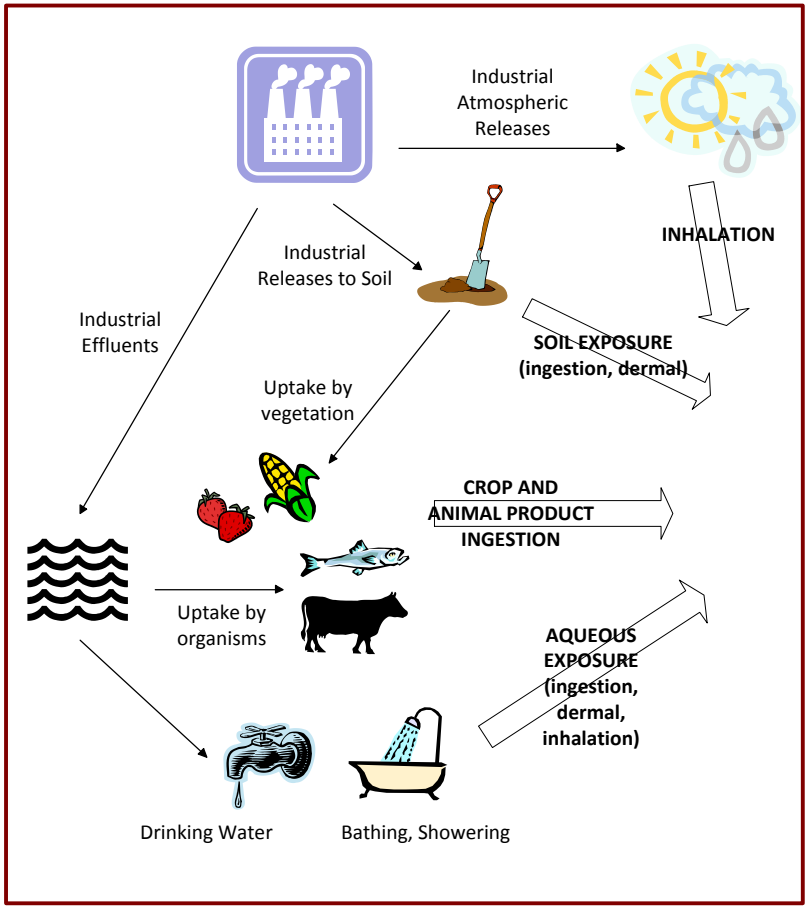
	Quantity (kg/year)	Number of Submitters	Sum of the Expert Ranked Use Code Indices
GPE	> 100 000	Top 10%	Top 10%
IPE	> 10 000	n.a.	Top 30%
LPE	Remainder	Remainder	Remainder

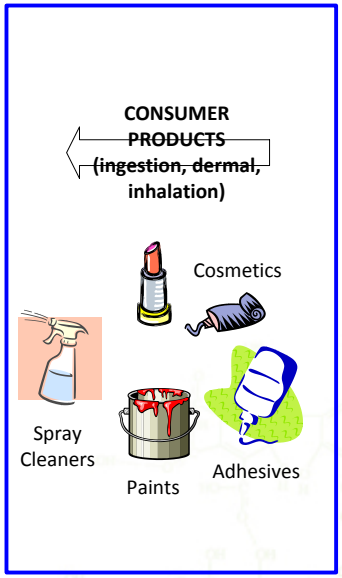
ComET – the Complex Exposure Tool

- Provides plausible upper bound quantitative estimates of combined consumer (nearfield) & multimedia environmental (farfield) exposure by duration and age group, taking into account:
  - "Sentinel" product scenarios
    - Uses for a particular chemical likely to result in highest exposure
  - Concentrations in environmental media of human exposure estimated based on extension of fugacity modelling

*** ComET tool not fully developed during categorization exercise, but methodologies later incorporated into screening assessment work

Far Field & Near Field Exposures





SimHaz Tool

- Applied to entire DSL
- Defined high or low hazard from classifications/assessments of other agencies based on weight of evidence
- Appropriate assessments selected based on comprehensiveness of review, peer review process, etc.

SimHaz Tool

- High Hazard Lists/Endpoints
  - Cancer (IARC, EU, HC, US EPA etc.)
  - Genotoxicity (EU)
  - Developmental Toxicity (EU)
  - Reproductive Toxicity (EU)

- Low Hazard Lists
  - PMRA 4a/US EPA 4a
  - OECD Low Concern

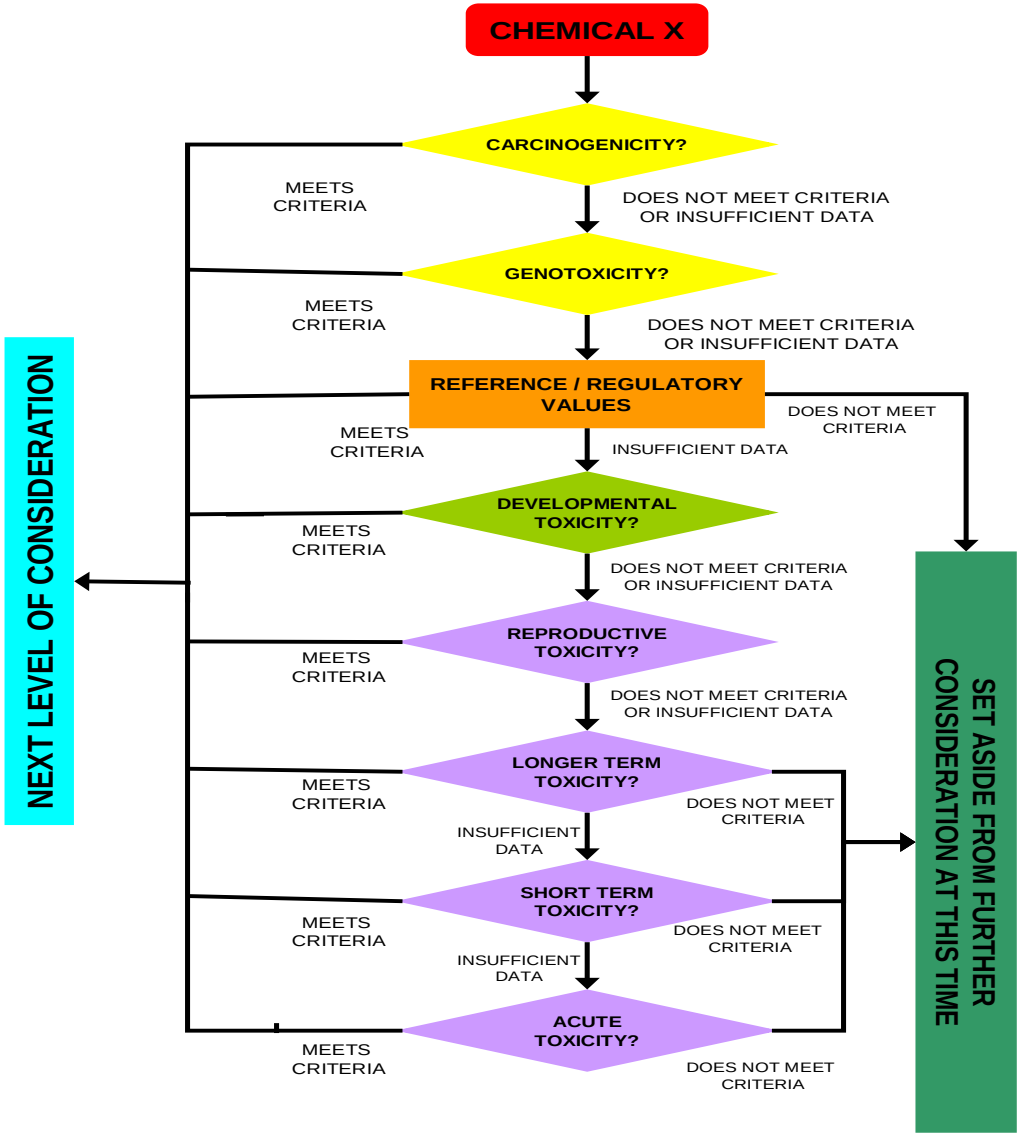
SimHaz Tool: Strengths and Limitations

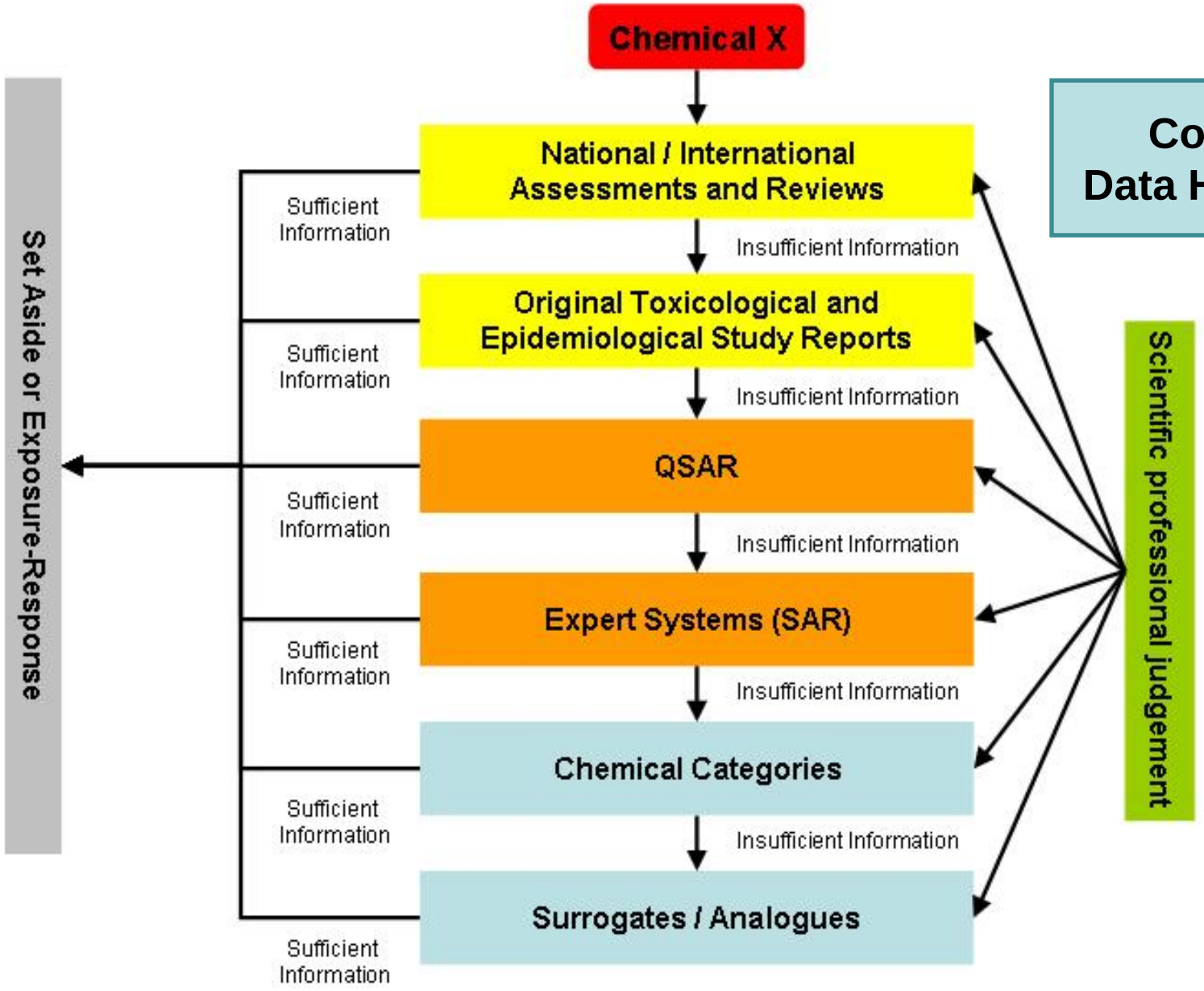
- Strengths
  - Efficient
    - Took advantage of critical review of others
  - Consistency
    - Assessments/classifications internationally
- Limitations
  - Bias towards data-rich substances

ComHaz Tool

- Hierarchical approach to consideration of:
  - Multiple endpoints relevant to characterization of hazard
  - Sources of relevant information

ComHaz Endpoint Hierarchy





ComHaz Data Hierarchy

ComHaz Tool – Endpoint-specific Criteria

(example subset – oral, NOAELs)

Endpoint	Information Source	Criteria
Cancer	Data or (Q)SAR	Positive evidence
Genotoxicity	Data or (Q)SAR	Positive evidence
Regulatory/Reference Value	International & National Assessments	Ref Value ≤ 0.1 mg/kg bw/day
Developmental Toxicity	Data	NO(A)EL ≤ 90 mg/kg bw/day
	(Q)SAR	Positive Prediction
Reproductive Toxicity	Data	NO(A)EL ≤ 10 mg/kg bw/day
Longer Term Toxicity	Data or (Q)SAR	NO(A)EL ≤ 10 mg/kg bw/day
Short Term Toxicity	Data	NO(A)EL ≤ 30 mg/kg bw/day
Acute Toxicity	Data or (Q)SAR	LD_{50} ≤ 500 mg/kg bw

ComHaz Tool- Endpoint Specific Guidance

Cancer

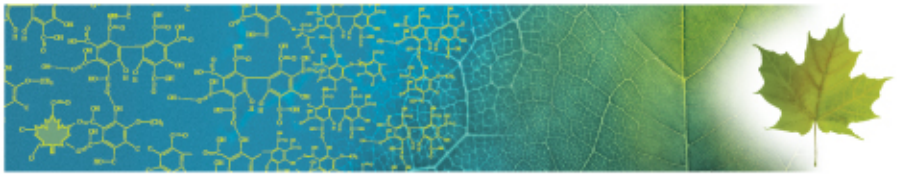
- Empirical data
  - Positive evidence = statistically significant increase in the incidence or prevalence of a specific tumour or an observed exposure-response relationship in animal or epidemiological study
  - Authors' conclusions generally accepted
  - Mode of action not considered

- QSAR modelling
  - Positive evidence = a valid QSAR prediction of sufficiently high probability in relevant model
  - Guidance for application/interpretation of models developed

ComHaz Tool- Endpoint Specific Guidance

Genotoxicity

- Criteria took into consideration
  - Predictive strength wrt concern for human health of
    - Endpoint investigated
    - in vivo versus in vitro tests
    - test data versus (Q)SAR models
- Extensive internal and external consultation, including expert workshop
- Conservative “one positive hit” approach adopted for initial categorization
- Exception – “sufficient” negative in vivo mammalian data could outweigh positive in vitro data
  - Defined as “negative results in two or more in vivo tests for different assays in two different tissues”



Tests/Endpoints Which Provide Sufficient Evidence for Genotoxicity to Warrant Further Consideration

Test Type	Endpoint	Examples
In vivo mammalian	Germ cell mutagenicity	Specific locus test, Transgenic mutation systems
	Germ cell clastogenicity or aneuginicity	Dominant lethal test, Heritable translocation test, Chromosomal aberrations in spermatocytes or spermatogonia, Spermatid micronucleus (centromere +ve or -ve), Oocyte cytogenetics, Sperm FISH assay, Abnormal chromosome segregation
	Germ cell DNA damage or repair	DNA adducts, Unscheduled DNA synthesis, Comet assay, Strand breaks
	Somatic cell mutagenicity	Mouse coat colour spot test, Transgenic mutation systems, Hprt mutations
	Somatic cell clastogenicity or aneuginicity	Chromosomal aberrations in bone maarrow or peripheral blood of rodents, Micronuclei (centroomere +ve or –ve) in bone marrow, peripheral blood or liver of rodents, Non-disjunction using FISH, Chromosomal aberrations in lymphocytes of exposed humans, Micronuclei (centromere +ve or –ve) in lymphocytes of humans
	Somatic cell DNA damage or repair	DNA adducts, Unscheduled DNA synthesis, Comet assay, Strand breaks
In vivo non-mammalian	Mutagenicity	Drosophila sex-linked recessive lethal test, Drosophila wing spot test
In vitro	Mutagenicity	Bacterial (Salmonella or E. coli), Mouse lymphoma TD assay, Hprt mutations, Human TK6 mutations
	Clastogenicity or aneugenicity	Chromosomal aberrations in human lymphocytes or rodent cells, Micronuclei (centromere +ve or –ve) in human or rodent cells, Mouse lymphoma assay (small colony mutants), Non-disjunction by FISH in human or rodent cells
	DNA damage or repair	DNA adducts unscheduled DNA synthesis, Comet assay, Strand breaks

Test Types Which Do Not Provide Sufficient Evidence for Genotoxicity to Warrant Further Consideration (indicator tests)

Test Type	Examples
In vivo mammalian	Sperm abnormality SCE or somatic cells Host mediated assays Inhibition of DNA synthesis
In vivo non-mammalian	Fish, plants, amphibians and birds
In vitro	SCEs Host mediated assay Cell transformation SOS assay Aneuploidy in yeast Inhibition of DNA synthesis

ComHaz Tool: Endpoint Specific Guidance

Regulatory Values

- Reference values or regulatory limits established by acceptable national or international agencies for provision of guidance for regulatory, advisory or risk management purposes

- Included:
  - Tolerable Intakes/Concentrations (TIs/TCs), Acceptable Daily Intakes (ADIs), Reference Doses/Concentrations (RfCs/RfDs) or Miminal Risk Levels (MRLs) for lifetime exposure on the basis of an effect level established for non-neoplastic effects observed in epidemiological investigations or studies in experimental animals.

- Not Included:
  - Reference values established for less than lifetime exposures (e.g., Acute Reference Dose, Acute Minimal Risk Level, Intermediate Minimal Risk Level, etc.) are not considered for the purposes of prioritization
  - Regulatory or reference values developed for occupational exposures (e.g.,Threshold Limit Value, Recommended Exposure Value, Short Term Exposure Limit, etc.)

ComHaz Tool: Strengths and Limitations

- Strengths
  - Health protective
  - Comprehensive
  - High confidence in “set asides”
  - No bias towards data rich substances
  - Designed for high throughput
  - Takes advantage of critical reviews of others
  - Significant contribution of QSAR component to priority setting
  - External input, consultation, peer review

- Limitations
  - Resource intensive

Results of Categorization

- Categorization/Prioritization completed in September 2006
- Identified priorities for further work/action based on concern for:
  - Environment
  - Human Health
  - Environment & Human Health
- Of the 23,000 substances on the DSL, 4300 identified as priorities
  - 4000 met the categorization criteria
  - 300 warranted further attention from a human health perspective

Combined Categorization Results

Health / Eco	GPE or IPE and HH	IPE	GPE	HH	Do not meet health criteria	Total
PBiT	26	22	4	16	325	393
PiT or BiT	80	189	89	64	2400	2822
Uncertain	3	207	63	11	2679	2963
Do not meet eco criteria	192	1206	449	249	14041	16137
Total	301	1624	605	340	19445	22315

Meet categorization criteria

Do not meet criteria, but further consideration

Do not meet criteria

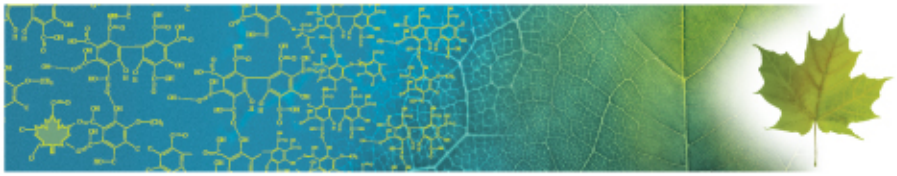
The Way Forward

- Categorization set the stage for assessing and managing chemicals in Canada, having provided the basis for an informed targeted approach to address the highest priorities from an ecological and/or human health perspective.

- The next step:

Launch of Canada's Chemicals Management Plan (CMP) in December 2006

Prioritization & Assessment: Past & Future

- Capitalize on past efforts to move forward on these substances through strengthened partnerships inside and outside the federal government to ensure the most efficient and effective protection of Canadians and their environment
  - Program expertise
  - Experienced stakeholder engagement relationships
  - Targeted legislative design
  - Triggers process for emerging priorities

QUESTIONS?