Screening Chemicals in Commerce to Identify Possible Persistent and Bioaccumulative Chemicals: New Results and Future Work

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Outline

- The “existing chemical” universe
- Assessments/categorization of chemicals in commerce
- Selected chemicals with P, B and POP characteristics from a combined USEPA/Canadian DSL dataset
- Review of Low/Medium Production Chemicals and chemicals that are potential biomagnifiers in air-breathing organisms
- Toxicity Reviews
- Future Pollution Prevention Studies
- Future challenges

The Universe of Chemicals

Globally

- With CAS numbers: **33,760,000** organic + inorganic substances (Feb/08)
- Commercially available: **19,184,000**
- Inventoried/regulated chemicals: **246,000**
- In commerce in USA, EU, Japan: **~100,000 with 30,000 > 1 t/yr**
- **Tracked by US EPA's Toxics Release Inventory: 650**
- **Routinely measured in environmental media: <1000**

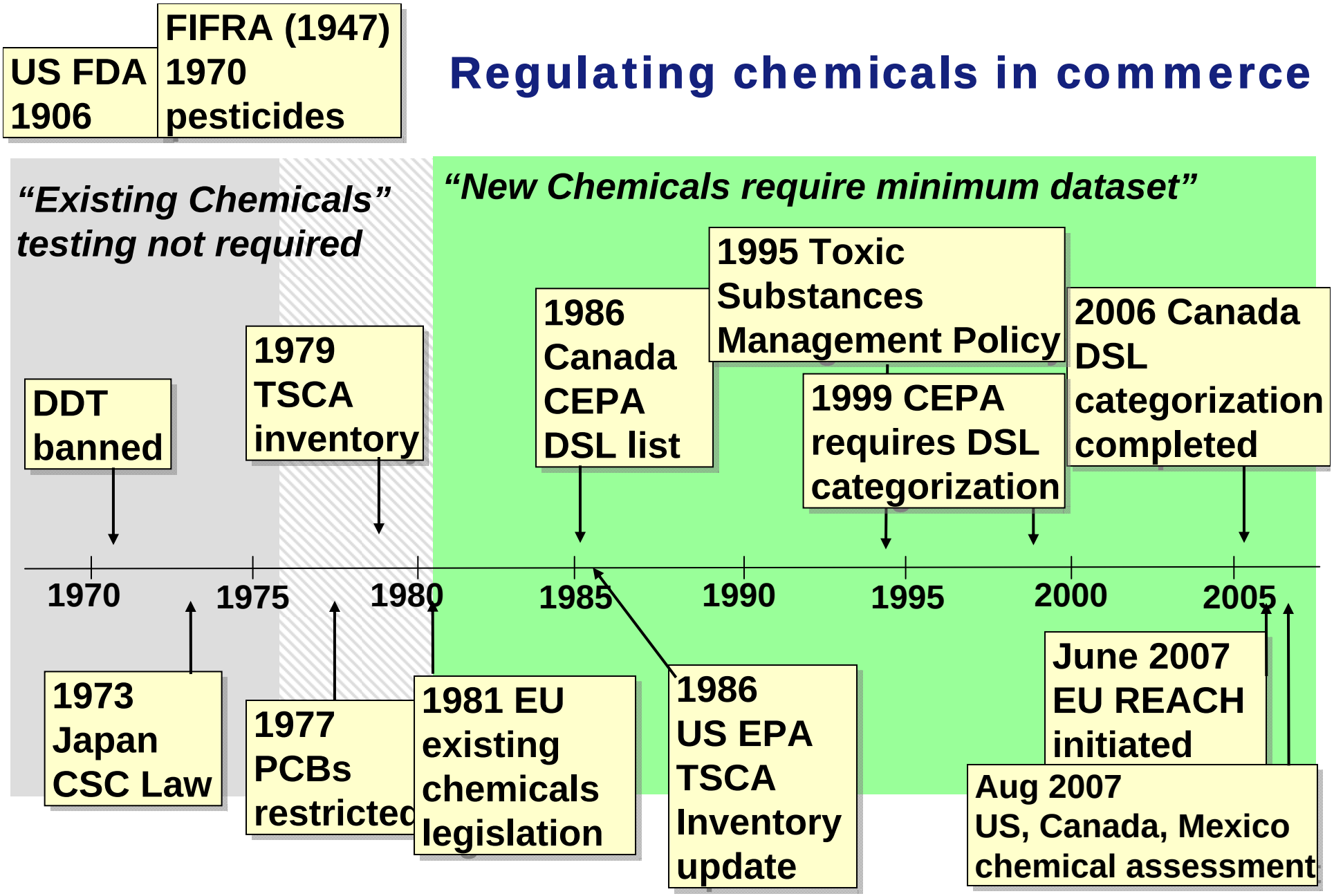
In Canada

- Domestic Substances List (DSL): 24,700 (established in 1986)
- DSL & Non DSL: 70,000 substances (as of 2006)

In USA

- Toxic Substances Control Act (TSCA) and TSCA Inventory update: originally 62,000 (1976), now ~82,000 substances

Regulating chemicals in commerce



~61,000 substances "grandfathered in"

~28,000 substances since 1976 or 1000 new substances per year

Screening of *existing chemical* lists is widening the data available for identifying potential P,B & T substances

- **TSCA Inventory Screening (US EPA)**
  - Inventory Update Rule (IUR) lists chemicals >454 t (10,000 lbs)/yr
  - Updates 1986, 1990, 1994, 1998, 2002, *2006*
  - 13,750 substances (all years)
- **US EPA High Production Volume Challenge Program**
  - 2800 chemicals
  - >1,000,000 lbs/yr
- **European "REACH" (Registration, Evaluation & Authorization)**
  - Evaluation of ~5000 substances with production >100 t/yr
  - Registration of ~30,000 substances produced at >1 t/yr
  - Came into force June 2007

Environment Canada's Domestic Substances List Categorization

- Mandated under CEPA 1999; completed September 2006
- 23,000 substances in production/use >100 kg/yr in 1986
- Screening of 11,300 organics with QSAR predicted properties + 1436 organics of unknown composition (UVCBs)
- Screening criteria: Persistent (P) or bioaccumulative (B), in accordance with Canadian P and B guidelines, and inherently toxic (iT) to humans or to non-human organisms, as determined by lab or other studies
- 4300 chemicals categorized for further assessment under the Chemicals Management Plan (CMP)

Goals of Our Study

- Develop a North American rather than Canadian list of potentially PB&T chemicals
  - — Greater relevance to the Great Lakes and trans-boundary long range transport than CMP priorities
- Using Quantitative Structure-Property relationships, and scientific judgment, identify chemicals in commerce that may be P and B and have not been previously measured in environmental media
- Assess whether selected chemicals can be analyzed by existing methods in use for POPs and new PB&T chemicals in the Great Lakes and the Arctic
- Analyze use and potential environmental release of new emerging contaminants
- Look for pollution prevention opportunities

Development of a Combined Canadian and US database of chemicals in commerce (Howard and Meyland 2007)

Source	No. substances	Reporting threshold	Reporting date
US EPA High production volume (HPV) program*	3549	1,000,000 lbs/yr (454 t/yr)	Post-1990
US EPA TSCA Inventory update rule (IUR) web site**	14,458 organics (combined HPV and EHPVs)	>10,000 lbs/yr (4540 kg/yr)	IUR reporting years; 1986 to 2002
Canadian DSL categorization***	11,317 organics	>100 kg	Mid-1980s
UVCBs**** (1400 on the DSL)	3059 organics	>100 kg	Mid-1980s
Total (after duplicates removed)	**22,043**		

*available from http://www.epa.gov/HPV/hpvchmlt.htm
** available from http://www.epa.gov/oppt/iur
*** available from Environment Canada - http://www.ec.gc.ca/substances/
**** UVCB = Unknown, of Variable Composition, or of Biological Origin – organic chemicals

Persistence and Bioaccumulation Characteristics of the 22,043 Chemicals Estimated Using EPISuite Version 3.12

Characteristics*	No.	%	Notes
log K_{ow} >5	4239	19%	Indicates tendency to adsorb to sediments and to bioaccumulate
BCF >2000 BCF >5000 BCF >50,000	924 566 19	4.6% 2.8% 0.1%	Bioaccumulation from water exposure – does not include biomagnification
AO* half-life >2 days AO half-life >10 days	1973 840	10% 4%	AO half-life indicates stability to atmospheric oxidation and potential long range transport
log K_{aw} >-5 and log K_{aw} <-1	6515	32%	K_{aw} describes air-water partitioning. Compounds with log K_{aw} >-5 & <-1 are "hoppers"
log K_{ow} ~2-5 and high log K_{oa} ~6-12	2000	10%	Biomagnification in air-breathing organisms (Kelley et al. 2007)

*K_{ow} = octanol water partition coefficient
BCF = bioconcentration factor predicted with EPIsuite software
AO= atmospheric oxidation half-life
K_{aw} = air-water partition coefficient

Further Prioritization Based on Lessons Learned from POPs in the Great Lakes and in the Arctic

1. High bioaccumulation/biomagnification potential, i.e., in top predators
2. Persistence – sequestered in bottom sediments in the open lakes implying a low rate of biodegradation
3. Long range transport potential i.e., found in mid-lake, in Lake Superior and remote lakes such as Siskiwit Lake
4. Quantity in use and potential for emissions i.e., open use or as an additive vs. as a chemical intermediate

Selection Characteristics	#	Notes
Predicted BCF >1000, **Atmospheric Oxidation >1 day, and Log Kaw >-5 and <-1**	105	Using EPIsuite. Mainly chemicals with LRT potential
By chemical class (Br, Cl, F, I, Si, cyclic HCs) and considering biodegradability	324	By expert judgment – includes chemicals and their degradation products with low LRT but potential for persisting in sediments and in the water column
Total	429	**70% halogenated; 10% siloxanes**

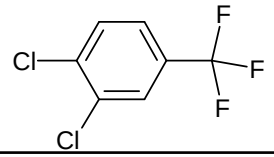
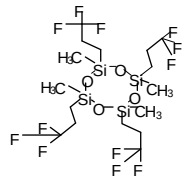
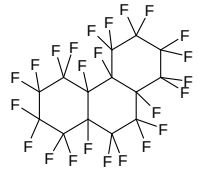
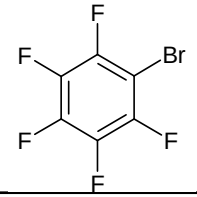
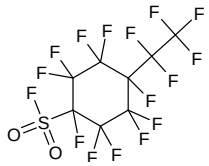
Information on Measurement and Analyzability of the 429 Substances

Analysable	Well monitored in the GL region and Arctic (i.e., programs such as IADN, NCP)	Chemicals that may have been analysed in any GL & Arctic measurement studies	Analyzable using existing methods for neutral POPs or other neutrals such as pesticides	Analyzable by LC-MS/MS ESI mode (anionic) or positive CI mode
Yes	16	83	280	46
% Yes	4%	19%	65%	11%
No	413	346	116	
Maybe			33	11

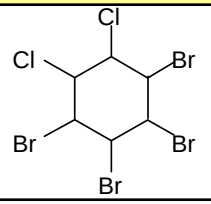
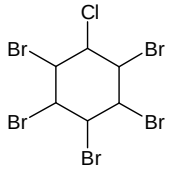
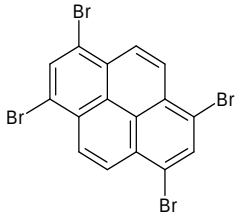
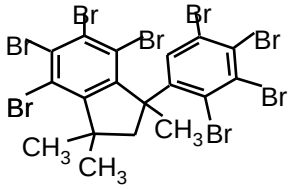
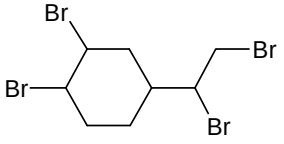
Further Prioritization of Low-Medium Production Volume and Potential Biomagnifiers in Air-Breathing Organisms

- Low-Medium Production Volume
  - Low: 10,000-500,000 lbs/yr
  - Medium: 500,000-1,000,000 lbs/yr
  - Total of low and medium = 9378 chemicals
    - » Scientific judgment screening = 270 chemicals
- Biomagnifiers in Air-Breathing Organisms
  - Low K_{ow} = ~2-5 and Log K_{oa} 6-12 = 2000 chemicals
    - » Scientific judgment screening = 95 chemicals
- Total Chemicals (429 +184) - 613
  - 62% are halogenated,
  - 27% are hydrocarbons or N or S containing HCs
  - 8% are siloxanes
  - 3% are P containing.

Some Semi-Volatile, Medium or High Production, Chlorinated or Fluorinated Organics of Potential Interest Due to (1) Predicted Persistence and/or Bioaccumulation and (2) Ease of Analysis

Substances	Predicted properties	Prod'n / yr (USA, lbs)	Structure	Notes
1,2-dichloro-4-(trifluoromethyl)-benzene	Log K_{ow} = 4.2 $AOt_{1/2}$ >100 d	1-10 M (2002)		Very P, highly volatile. Intermediate in pesticide production
Trifluoropropyl methyl cyclotetrasiloxane	Log K_{ow} = 10.7 $AOt_{1/2}$ >?	0.5-1.0 M (2002)		P, low predicted BCF
Perfluoroperhydro-phenanthrene	Log K_{ow}= 9.6 $AOt_{1/2}$ = ?	0.010-0.5 M (2002)		Looks very P and B
Tetrafluorobromo-benzene	Log K_{ow}= 3.9 $AOt_{1/2}$ = 85 d	0.010-0.5 M (1998)		Looks P and B
Cyclohexane-sulfonyl fluoride and sulfonate	Log K_{ow}= 5.9 $AOt_{1/2}$ = 77 d	0.010-0.5 M (2002)		P and possibly B as sulfonate deg'n product

Some Brominated Organics of Potential Interest Due to Production Volume, High Predicted P & B and Ease of Analysis

Substances	Predicted properties	Prod'n / yr (USA, lbs and last year rep'd	Structure
Tetrabromo-dichloro-cyclohexane	Log K_{ow} = 4.6 P & B	>10-500 k (1998)	
Pentabromo-6-chloro-cyclohexane	Log K_{ow} = 4.7 P & B	>10-500 K (2002)	
1,3,6,8- tetrabromopyrene	Log K_{ow} = 8.5 Persistent May not be B	>0.5-1M (2002)	
Octabromo-1,1,3-trimethyl-3-phenyl indan	Log K_{ow} ~10 P & B	>0.5–1 M (2002)	
1,2-dibromo-4-(1,2-dibromoethyl)cyclohexane	Log K_{ow} = 5.2 P & B	>10-500 K (2002)	

Toxicity Estimates of Priority Chemicals

- 429 chemicals in commerce previously identified as having potential for persistence and bioaccumulation in the Great Lakes

- Further evaluated to identify and estimate whether these compounds are toxic to aquatic organisms and to mammals utilizing:
  - Analog Identification Methodology (AIM)
  - ECOSAR
  - OncoLogic

AIM

- EPA is currently developing the AIM tool to identify close analogs that have measured data
- Designed to help identify publicly available, experimental toxicity data on closely related chemical structures
- AIM database contains 31,031 potential analogs with publicly available toxicity data
- Experimental data sources Indexed
  - On-Line Databases
    - » TSCATS, HSDB, IRIS
  - U.S. Government Documents
    - » NTP, ATSDR, HPV Challenge Program
  - Other Sources
    - » DSSTox, RTECS, IUCLID, AEGLS

AIM Results

- The AIM tool was run to identify if a chemical is in one of the approximately 45 EPA Chemical Classes used by the New Chemicals Program under TSCA
  - These 45 chemical classes have been identified as being of potential concern for human health effects

- 277 chemicals were included in the 45 chemical classes
- 152 chemicals were not in the 45 chemical classes

ECOSAR

- ECOSAR is a computerized program for aquatic toxicity estimates that is currently used by EPA's Office of Pollution Prevention and Toxics (OPPT)
- Part of the EPISuite™ software – provides estimates of potential for aquatic toxicity based up K_{ow} and chemical class
- To date, over 150 SARs have been developed for more than 50 chemical classes
- This analysis involves the application of SARs (Structure Activity Relationships) to predict the aquatic toxicity of chemicals (LC_{50}, EC_{50}, chronic, etc.) for various aquatic organisms (fish, daphnid, algae, etc.)

ECOSAR Results

- The most toxic value (i.e., lowest LC_{50}) for each chemical was selected as is done with the New Chemicals Program under TSCA and by Environment Canada

- Value was given for 349 out of 429 chemicals
  - Chemicals were excluded when it was predicted that the chemical may not be soluble enough to meet the predicted toxic effect (i.e., LC_{50})

OncoLogic

- The OncoLogic program was run on each chemical that a structure was available for in the program
- The program assigns a baseline concern level from high to low for a chemical to have the potential to cause cancer
- The chemical analog structure activity method was used with some standard exposure scenarios selected

OncoLogic Results

- OncoLogic
  - 146 chemicals were successfully run
    - High = 0
    - High-Moderate = 10
    - Moderate = 24
    - Low-Moderate = 34
    - Marginal = 29
    - Low = 49

- 32 chemicals had pre-existing cancer screening (i.e., IARC, NTP, etc.)

Fate, Transport and Exposure Potential

- Divide Priority Chemicals into Chemical or Use Classes
  - e.g., Chemical classes – Fluorinated, Brominated, Chlorinated, Siloxanes,
  - e.g., Fragrances, rubber chemicals, solvents, chemical intermediates, flame retardants
- High release – plasticizers, hydraulic fluids, or solvents, fire fighting surfactants, fragrances
- Degraded during use – antioxidants, vulcanizing agents, UV stabilizers, polymer initiators
- Stable during use – auto wax, defoaming agents, soil repellant
- Analyze Physical Properties, Binding, Release
  - Collect from PHYSPROP or Estimate with EPI Suite
  - Determine if chemically bound (reactive flame retardants vs. non-reactive)
  - Integrate physical properties & form during chemical use to assess release (use past examples of chemical release of know contaminants)

Pollution Prevention

- Need Variety of Approaches Dependent Upon the Use and Chemical Properties Required for the Application
  - —Synthetic intermediate: develop different synthetic route
  - —Solvent: examine physical properties (vapor pressure, solubility for application)
  - —Surfactant: same surfactant properties but more biodegradable
  - —Flame retardant: possibly use phosphate to quench flame rather than halogens
  - —General: structurally redesign molecule to make less persistent (less fully halogenated, linear alkyl chains – more biodegradable) but keep essential properties for use

The Emerging Challenge

Confirming SAR predictions with environmental measurements for priority PB&T chemicals

Analytical Method development
- **new or refinements of existing extraction and isolation procedures**
- **analytical standards and reference materials**

Instrument technology
High resolution separations & mass measurement
2D-GC-TOF, LC-MS/MS and LC-QTOF

Contaminant free reagents
Clean room isolation

Bioanalytical Methods and directed bioassays

"*in silico*" technology – computational toxicology
Improved QSARs to identify P,B&T parent and metabolites

e.g., metabolites via TIMES (tissue metabolism simulator), CATABOL, BIOWIN

Challenges and Opportunities

- Our screening of 000s of substances e.g., DSL and TSCA Inventory has yielded some interesting probable P&B substances
- Uncertainties in this type of screening include:
  - Possibility of **false positives** and **false negatives**
  - Lack of information on uses and actual emissions of the chemicals
  - Need for information on degradation products
- Lack of information on **biological effects** of the selected chemicals
- Numerous opportunities for both environmental chemists and environmental toxicologists
  - Analytical and bioanalytical methodologies
  - Exposure and risk assessment
  - SAR development
  - Chemical fate modeling

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