Holistic Mass Balance Modeling Approach for Chemical Screening and Priority Setting

EPA Exposure Science Community of Practice (ExpoCoP)
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Overview of presentation

• Rationale / background
• Risk Assessment, IDentification And Ranking (RAIDAR)
  – Screen and prioritize organic chemicals with greatest exposure, hazard and risk potential to humans and the environment
  – Illustrate key concepts of RAIDAR model
  – Illustrative applications for risk priority setting of ~1,100 Canadian Domestic Substances List (DSL) chemicals
• Holistic vs. current “PBT” screening methods
• Model comparisons with monitoring data (PBDE 99)
• Addressing uncertainty
• Farfield Human Exposure (FHX) model
• Questions
Exposure and risk assessment: concept

Chemical emissions

Environmental fate/transport, distribution, degradation, food web bioaccumulation and exposure to environmental receptors and humans

Mackay 2001
Rationale: chemical assessments

• Regulatory programs require the assessment of a large number of chemicals (~100,000), e.g., UN Stockholm Convention, Canadian Environmental Protection Act 1999, TSCA, REACH

• Methods and criteria developed in 70s and 80s now being applied to screen and prioritize chemical lists

• Typical current approach is PBT “bright line” categorization

• Enormous task with little measured data available, limited resources and it is not practical to measure “everything” ($$, animal testing, people power)
Measured data for organic chemicals on Canada’s DSL ~11,000 organics

- Limited monitoring data (“legacy pollutants”)
- Lab tests of chemical degradation <7%
- Lab BCF data in fish, i.e., no dietary uptake, <4%
- Acute toxicity data in aquatic species <10%
- Physical-chemical properties:
  - Vapour pressure <5%; Aqueous solubility <5%; $K_{OW}$ <10%

- Quantitative structure-activity relationships (QSARs) and mass balance models are needed…
General objectives

• Develop a mass balance modelling framework for estimating exposure and risk potential to identify and rank organic chemicals for more comprehensive assessments (monitoring and modelling)

• Bring together available information on chemical partitioning, degradation, fate and transport, food web bioaccumulation, exposure and effect in a transparent and “holistic” model

• Save uncertain actual emissions information for the last step in the exposure and risk calculations
RAIDAR evaluative model

Multimedia mass balance exposure and risk assessment model
~ EUSES, CalTOX, but different; notably the treatment of food web bioaccumulation (Birak et al. 2001)

1. Physical component (Air, Water, Soil, Sediment)
   – Regional scale environment, i.e., $10^5$ km$^2$
   – Level II or III fate calculations (“box” models)

2. Biological component
   – “Representative” ecological and human receptors, flexible selection of biological properties
   – Mechanistic mass balance food web bioaccumulation models
     • Aquatic, terrestrial, agricultural species
     • Chemical specific biomagnification and biotransformation
RAIDAR exposure, hazard and risk metrics

- RAF – Risk Assessment Factor
- HAF – Hazard Assessment Factor
- EAF – Exposure Assessment Factor
- BAF – Bioaccumulation Factor
- $iF$ – intake fraction, intake rates
- TBB – Total Body Burdens, internal dose
- $P_{OV}$ – Overall Persistence
RAIDAR evaluative environment

Level II or Level III fate calculations

Air

Soil

Water

Sediment

Environ Sci & Technol 40, 2316-2323
Vegetation models

Foliage vegetation

Root vegetation

\[ \log \left( \frac{C_{\text{FV}}}{C_{\text{GA}}} \right) \] vs. \[ \log K_{\text{OA}} \]

\[ \log (\text{BCF root kg.kg}^{-1} \text{ww}) \] vs. \[ \log K_{\text{OW}} \]

- DDs_DFs
- CBs_PCBs
- PAHs

- CBs_UK_carrots
- PAHs_UK_potatoes
- PAHs_UK_carrots
- PAHs_Greece_carrots
- HCHs_DDX_China_various

*Environ Sci & Technol* 42, 4648-4654
Bioaccumulation Model

Water ventilating organisms ($K_{OW}$)

Empirical biomagnification factors – capture biomagnification potential
Absorption, Metabolism, Elimination – assumed a “well mixed compartment”
Bioaccumulation Model

Air breathing organisms ($K_{OW}$ and $K_{OA}$)

- Absorption, Metabolism, Elimination – assumed a “well mixed compartment”

Empirical biomagnification factors – capture biomagnification potential
Running the model

• Input requirements:
  – Physical-chemical properties: $K_{OW}$, $S_W$, VP, pKa
  – Half-lives: biodegradation, biotransformation, hydrolysis, oxidation, photolysis
  – Consistent Toxicity or Threshold endpoint for risk ranking – $C_T$ (e.g. critical body residue)

• Unit emission rate – $E_U$ (kg/h)
  – Arbitrary value, “seeds” the model (e.g. 1 kg/h)
  – Circumvents initial need for actual emission rate – $E_A$ (kg/h)
e.g., pyrene fate and distribution calculations
Pyrene food web calculations ("unit" exposure)

- Log (CU mol.m⁻³) values for various organisms:
  - Human
  - Dairy
  - Beef
  - Poultry
  - Avian Omnivore
  - Terrestrial Carnivore
  - Terrestrial Herbivore
  - Aquatic Mammal
  - Fish
  - Soil Invertebrate
  - Benthic Invertebrate
  - Plankton
  - Root
  - Foliage

The Benthic Invertebrate has the highest log (CU mol.m⁻³) value.
Risk calculations (e.g.)

• Unit concentrations in all biota $C_U$ (mol/m$^3$)
• Hazard quotients for all biota, i.e., $HQ = C_U / C_T$
• Identify most sensitive receptor, i.e., $HQ_{max}$
• Back-calculate the ‘critical’ emission rate
  – i.e., $E_C = E_U / HQ_{max}$
• Risk Assessment Factor (RAF) = $E_A / E_C$
  – High RAF — high concern
  – Allows for priority ranking based on risk, i.e., 1….n
Prioritizing risk: a case study

- 1,100 Canadian DSL organic chemicals
- $E_U = 1 \text{ kg/h}$
- $E_A$ DSL quantity estimates
- Selected effect endpoint
  - $C_T$
  - DSL acute lethality data
  - Critical body residues
Prioritizing risk: $n = 1,100$

Chemical ID #
## Prioritizing risk

<table>
<thead>
<tr>
<th>RIB</th>
<th>LII Count</th>
<th>LIII A,W,S Count</th>
<th>LIII Air Count</th>
<th>LIII Water Count</th>
<th>LIII Soil Count</th>
<th>Average frequency</th>
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<td>G</td>
<td>309</td>
<td>40</td>
<td>281</td>
<td>77</td>
<td>235</td>
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</table>

Average frequency for all RIBs: $n = 1,100$
Screening and priority setting methods

Current POP and PBT screening and “priority setting” methods (ca. 1970s-1980s):

1. Hazard assessment: multiple categories (PBT), “bright line cutoff” criteria, e.g., “B” or “not B”; screened “in” or “out”

2. Risk assessment: (exposure/effects, uncertainty) for those chemicals screened “in”

Binary scoring in multiple categories makes it difficult to assign priorities: “is a P&T worse than a B&T?”
Hazards and QSARs

Example of typical “bright line” PBT assessment:

1. Persistence: Level II or III fate model using estimated phys-chem properties and biodegradation half-lives, media of concern air:
   - AOPWIN $t_{1/2\text{-air}}=1.8$ d, criterion is 2 d: “not P”

2. Bioaccumulation: $K_{OW}$-QSAR estimate into BCF or BAF model:
   - BCF or BAF = 4800, criterion is 5000: “not B”

3. Toxicity: QSAR-aquatic toxicity model:
   - LC50 = 0.5 mg/L, criterion is 1 mg/L: “T”

Is it a hazard? Is it a risk? Uncertainty??
Canada is the first to conduct PBT assessments on existing chemicals

Canadian DSL ~23,000 chemicals (~11,000 organics)

Meet criteria DSL “in” or DSL(I)
~4,000 “further attention”

Doesn’t meet criteria DSL “out” or DSL(O)
~19,000 “no further action”

Risk assessments are projected until 2025 and beyond
“Holistic” risk calculation

Risk is essentially a function of 3 major components:

1. Chemical emission to the environment (Q or $E_A$; mol/h)
2. Exposure or “delivery” (P&B, $D$; h/m$^3$)
3. Threshold level (toxicity) ($T$; m$^3$/mol or $1/C_T$)

Risk Assessment Factor:

$RAF = E_A DT = \text{exposure/effect (uncertainty)}$
Holistic hazard and risk calculations

Combine elements of exposure, hazard and risk in a coherent mass balance modelling framework for holistic screening methods

1. Risk Assessment Factor (RAF) \approx f(Q,P,B,T)
2. Hazard Assessment Factor (HAF) \approx f(P,B,T)
3. Exposure Assessment Factor (EAF) \approx f(P,B)

Calculate single values for transparent chemical comparisons for ranking and priority setting based on exposure potential, “combined hazard” or risk objectives
Policy Analysis: current vs holistic methods

Current methods: Canadian DSL categorization; chemicals screened “in” or “out” based on PBT values and bright line cut-off criteria

Holistic methods: RAIDAR EAF, HAF and RAF calculations

Chemicals selected for a case study:

- 100 DSL chemicals “in” – DSL(I), “further attention”
- 100 DSL chemicals “out” – DSL(O), “no further action”
- 12 Stockholm Convention POPs (benchmark)

1. Use same basic information available for the categorization for RAIDAR calculations, i.e., “no biotransformation”

2. Include estimates for biotransformation using novel QSAR
Delivery – D; maximum EAF (P,B): all species

- POPs + DSL(I) – DSL(O)

\[ \text{log (D h.m}^{-3}) \]

\( \sim 15\% \)

\( \sim 20\% \)
Hazard (P,B,T)

- HAF_POPS + HAF_DSL(I) - HAF_DSL(O)
Hazard (P,B,T)

- HAF_POPS + HAF_DSL(I) - HAF_DSL(O)

~75% overlap

Environ Sci & Technol 42, 4648-4654
Risk (Q,P,B,T)

- HAF_POPS + HAF_DSL(I)
- HAF_DSL(O)
+ RAF_DSL(I)
- RAF_DSL(O)

Environ Sci & Technol 42, 4648-4654
Risk (Q,P,B,T)

- HAF_POPs + HAF_DSL(I) - HAF_DSL(O) + RAF_DSL(I) - RAF_DSL(O)

~85% overlap for RAFs!

Environ Sci & Technol 42, 4648-4654
Predicting biotransformation

- Assuming negligible biotransformation is an “overly conservative” assumption, particularly for chemicals subject to biotransformation.

- Biotransformation rate data are needed for hazard and risk assessment to reduce “false positives”.

- A QSAR was developed and evaluated to predict primary biotransformation rate constants from chemical structure using in vivo biotransformation rate constant estimates for ~700 chemicals in fish.

- U.S. EPA’s EPI Suite Ver. 4.0
Human total body burden ($TBB$) predictions: influence of biotransformation assumptions

- Level III emissions to water

$\circ$: POPs; $\oplus$: non POPs

$TBB$ predictions:
- No biotransformation assumed
- Biotransformation included

$\sim 10^8$ difference in $TBB$ when estimates included

Environ Toxicol Chem in press
Risk (Q,P,B,T including biotransformation)

$\text{log } RAF$

+ RAF_Biotrans_DSL(I)  - RAF_Biotrans_DSL(O)
Risk (Q,P,B,T including biotransformation)

~95% overlap for RAFs!
## Priority setting methods summary

<table>
<thead>
<tr>
<th>Current methods</th>
<th>Proposed holistic methods</th>
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</thead>
<tbody>
<tr>
<td>Category based screening for priority assessment</td>
<td>Holistic strategy for exposure, hazard, and risk</td>
</tr>
<tr>
<td>Screening pass/fail values against cut-off criteria for P, B, T and Q</td>
<td>No bright line criteria</td>
</tr>
<tr>
<td>determines further assessment outcomes, e.g., BCF ≥5,000 is “B”; BCF &lt;5,000</td>
<td>No judgment required for multiple binary outcomes</td>
</tr>
<tr>
<td>is “not B”</td>
<td>Direct chemical comparisons for exposure, hazard and risk</td>
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<tr>
<td>Multiple binary assessments require judgment, e.g., “P and T; not B” or</td>
<td>Reliability of category criteria not a factor</td>
</tr>
<tr>
<td>“T; not P and B”</td>
<td>Uncertainty can be included for hazard, exposure, and risk</td>
</tr>
<tr>
<td>Reliability of category criteria determines further assessment outcomes,</td>
<td>Provides guidance for monitoring and green chemistry</td>
</tr>
<tr>
<td>e.g., B criteria do not exist for air-breathing organisms</td>
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<tr>
<td>Type I and II error potential high in screening stages, e.g., BCF = 5,100</td>
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<tr>
<td>vs. 4,900; or t&lt;sub&gt;1/2&lt;/sub&gt; air = 2.1 d vs. 1.9 d</td>
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<tr>
<td>Uncertainty not considered until risk assessment stage</td>
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</table>
Implications

• Based on available information current chemical assessment methods are not effective at setting priorities for risk assessment

• Potential for errors using current methods is high meaning limited resources will be “mis-applied” to chemicals of low risk while chemicals with high risk potential may not be evaluated

• Complementary holistic methods can enhance current chemical assessment efforts by focusing assessment on chemicals that pose the highest risks (better emissions estimates and toxicity data)

• Policies need to adapt as the science evolves (“70s-80s”)


RAIDAR evaluation

• Difficult to “validate” evaluative models, e.g.,
  ▪ Monitoring data are limited
  ▪ RAIDAR is not “site specific”, “representative conditions”
  ▪ Spatial and temporal issues (heterogeneity, steady-state)

• Case study for commercial pentabromodiphenyl ether (PBDE-99)
• Determine realistic “actual” emission rate estimate ($E_A$) for a regional scale “source” environment
• Exploit linearity of the model to scale “unit emission” predictions to expected concentrations in the real world using more “realistic” estimates for emissions
• Compile monitoring data for PBDE-99 in various environmental media (air, water, fish, meat products, humans, etc)
• Compare model predictions with monitoring data
PBDE 99: monitoring data (o) / model (x)

Air (pg/m³)
Water (pg/L)
Soil (ng/g dwt)
Sediment (ng/g dwt)

log concentration

-5 -4 -3 -2 -1 0 1 2 3
PBDE 99: monitoring data (o) / model (x)

Humans
Marine mammals
Piscivorous birds & eggs
Starlings
Dairy products
Meat products
Chickens
Various fish (monitoring)
Shellfish

log concentration (ng/g lwt)
PBDE-99 model and monitoring data

RAIDAR log predicted vs. log monitoring concentrations

- Air, water, soil, sediment
- Ecological compartments
- Human

1:1 line
Including uncertainty in predictions

- Propagation of uncertainty in exposure and risk assessments
What dictates uncertainty in the RAF?

\[
\text{RAF} = \frac{E_A}{E_U} \cdot \frac{C_U}{E_U} \cdot \frac{1}{C_T}
\]

- Quantity emitted
- RAIDAR estimate of environmental Delivery
- Toxicity of most sensitive receptor

- Each of these three “terms” is associated with uncertainty
- Actual emissions, i.e., “\(E_A\)” or “\(Q\)”; proportional
- \(1/C_T\) is indicator of toxic potency, i.e., “\(T\)”; proportional
- Fate, transport and bioaccumulation, i.e., “\(D\)” or \(C_U/E_U\) model state variables and inputs of phys-chem properties, half-lives (“\(P&B\)”)
Prioritizing uncertainty:

Which are the most sensitive and uncertain parameters?
What research effort will get the most “bang for the buck”?
FHX Model
Farfield Human Exposure Model

For screening level assessments of human exposure

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Version 1.01

New Features
## Health Canada Age Classes

### Human Properties

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<th>Diet</th>
<th>Food Sources</th>
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**NOTE:** Changes may be made ONLY to the Food Sources but changes will only be retained until the program is shut down. Changes are NOT saved.

**OK** **Cancel** **Help**
## Human Exposure

### CAS: 71432

**Benzene (BZ)**

#### Sample Environment

#### Overview

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<th></th>
<th>Nursing</th>
<th>Baby - Formula</th>
<th>Toddler</th>
<th>Child</th>
<th>Teen</th>
<th>Adult</th>
<th>Retiree</th>
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<td>7.15E-11</td>
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#### Intake Fraction

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<tr>
<td><strong>Population</strong></td>
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<td>3.69E-07</td>
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<td><strong>Total</strong></td>
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*Health Canada Age Class Specific Intake*
Some RAIDAR and FHX assumptions

• Steady state (not dynamic)
• Rate processes follow 1st order kinetics
• Results are based on “representative conditions”
• “Farfield” exposures to humans

Some limitations

• Most discrete organic chemicals (SMILES)
• Not recommended for pigments and dyes, and perfluorinated surfactants, strong acids and bases
• Need to improve for chemicals that appreciably dissociate at environmental and physiological pH
Summary

• Information on chemical partitioning, fate/transport, bioaccumulation, exposure and effect endpoint are brought together in a coherent mass balance framework
• Framework is adaptable
• RAF rankings span >14 orders of magnitude providing priority guidance for more comprehensive assessment and monitoring
• Fast and affordable for large scale screening using available data, revisit rankings as better data become available
• Uncertainty is inherent whether the data are measured or modelled and uncertainty can not be totally eliminated
• Key parameters can be identified to reduce uncertainty
• Assessing risk is the fundamental objective of regulatory programs
• Most chemicals can and should be screened for potential risks
Some on-going and future research

- Indoor exposures to humans
- Refined treatment for dissociating substances
- Plant uptake models
- Absorption efficiency models
- Biotransformation rate estimation
- Biodegradation rate estimation
- Toxicity models
- ...

Please visit The Canadian Centre for Environmental Modelling and Chemistry (CEMC) for a list of publications and model downloads

www.trentu.ca/cemc
Thank you for your interest and attention!

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