Holistic Mass Balance Modeling Approach for Chemical Screening and Priority Setting

EPA Exposure Science Community of Practice (ExpoCoP)

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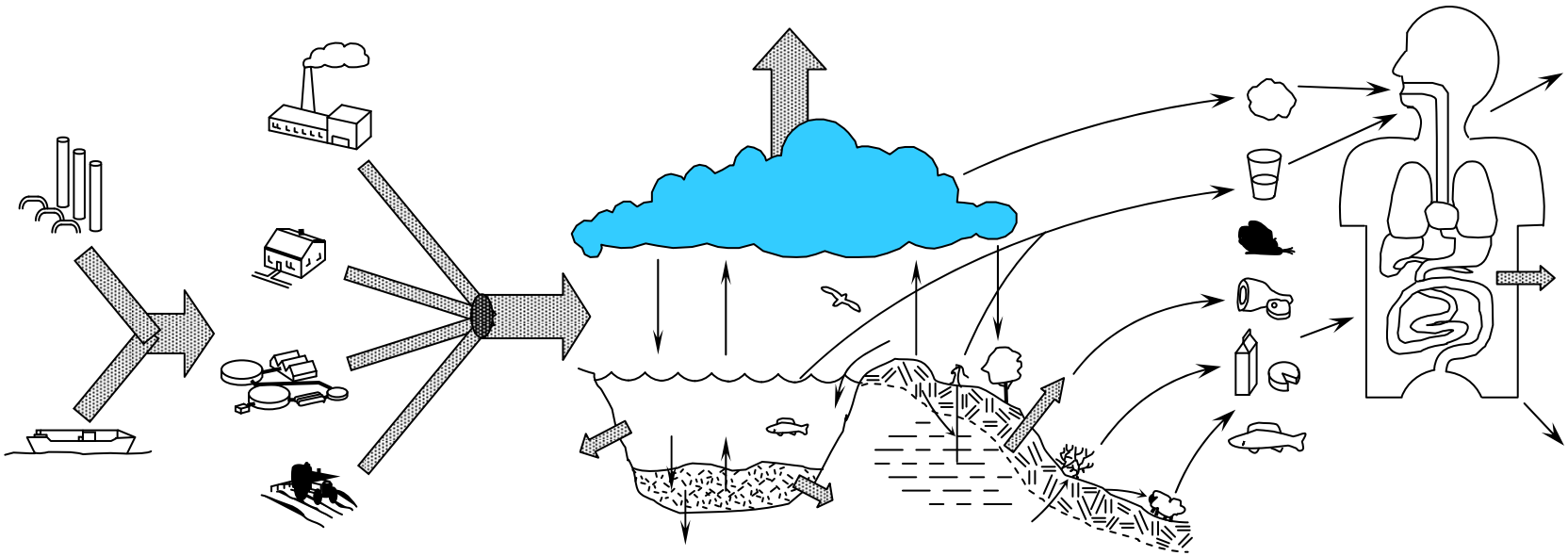
Overview of presentation

- 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)

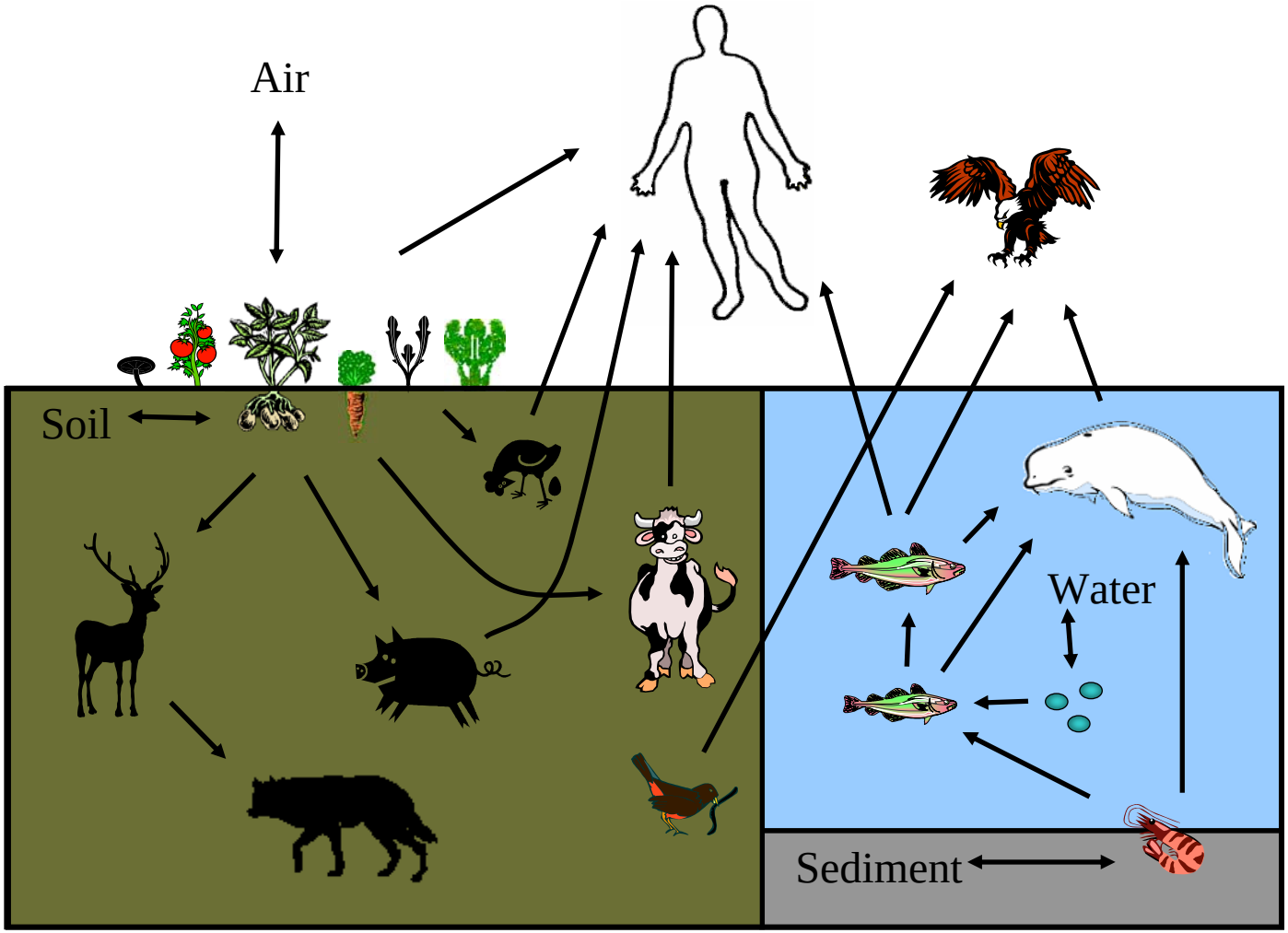
1. Physical component (Air, Water, Soil, Sediment)
   - – Regional scale environment, i.e., 10^5 km^2
   - – Level II or III fate calculations (“box” models)
2. Biological component
   - – “Representative” ecological and human receptors, flexible selection of biological properties
   - – Mechanistic 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

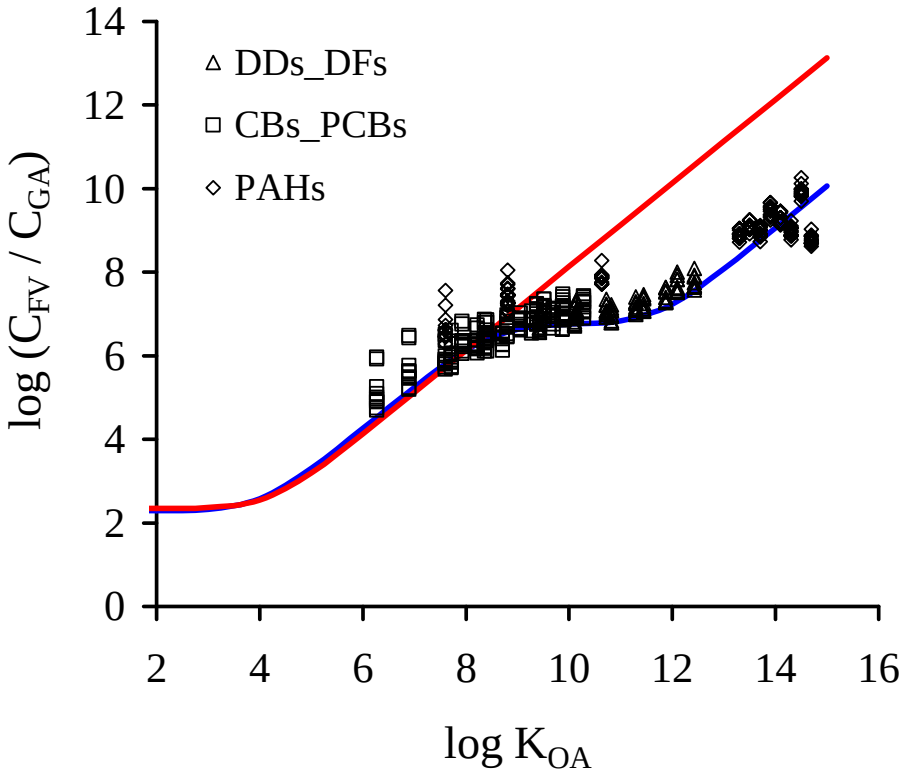
Level II or Level III fate calculations



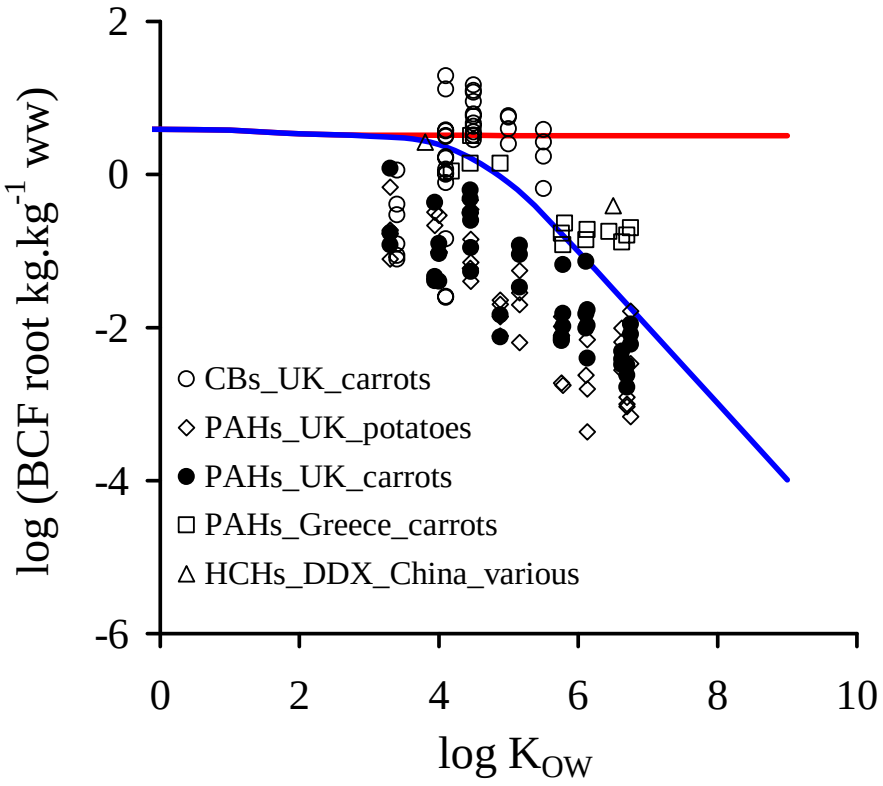
Environ Sci & Technol 40, 2316-2323

Vegetation models

Foliage vegetation



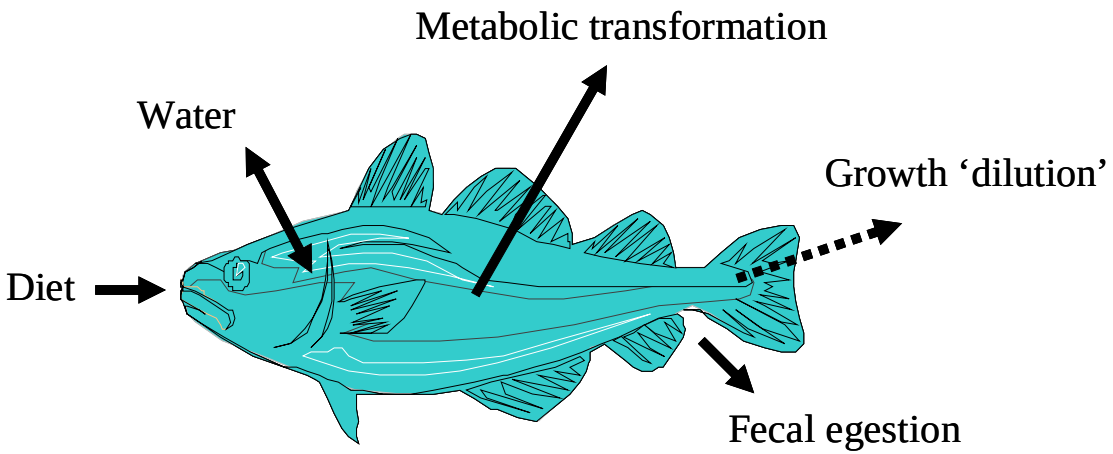
Root vegetation



Environ Sci & Technol 42, 4648-4654

Bioaccumulation Model

Water ventilating organisms (K_{OW})

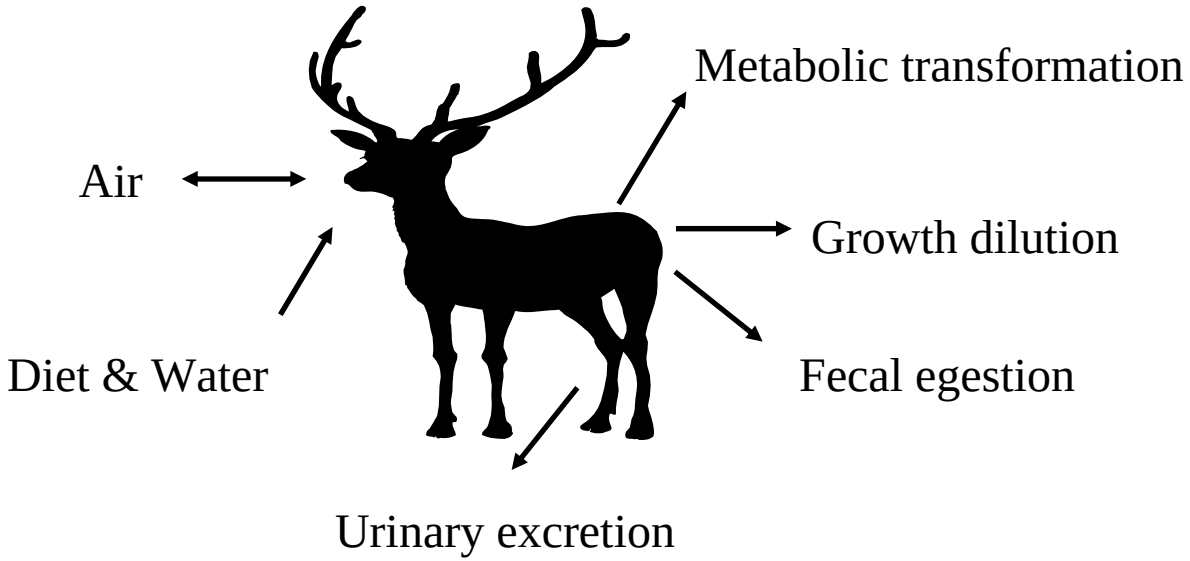


Empirical biomagnification factors – capture biomagnification potential

Absorption, Metabolism, Elimination – assumed a "well mixed compartment"

Bioaccumulation Model

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



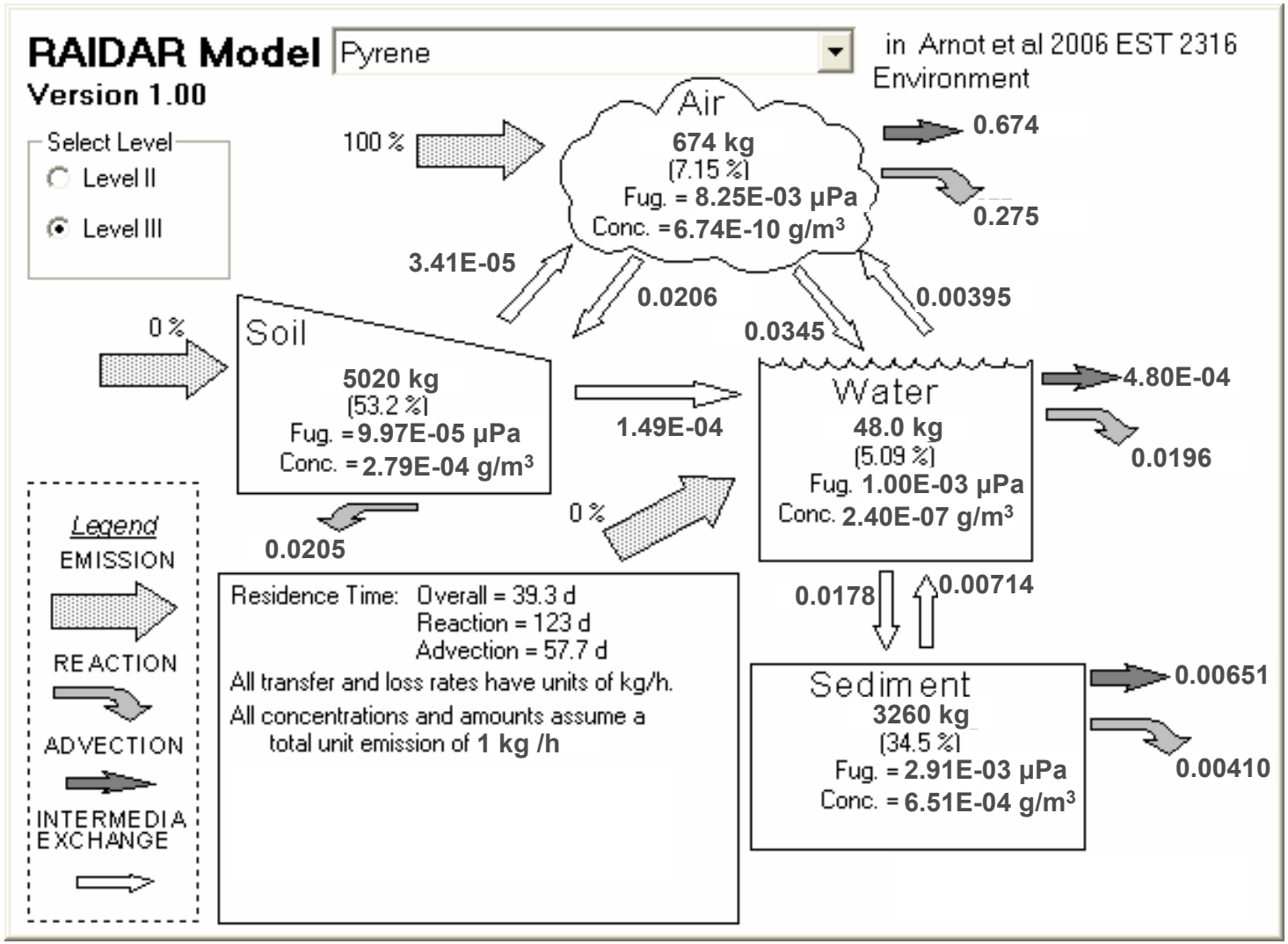
Empirical biomagnification factors – capture biomagnification potential

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

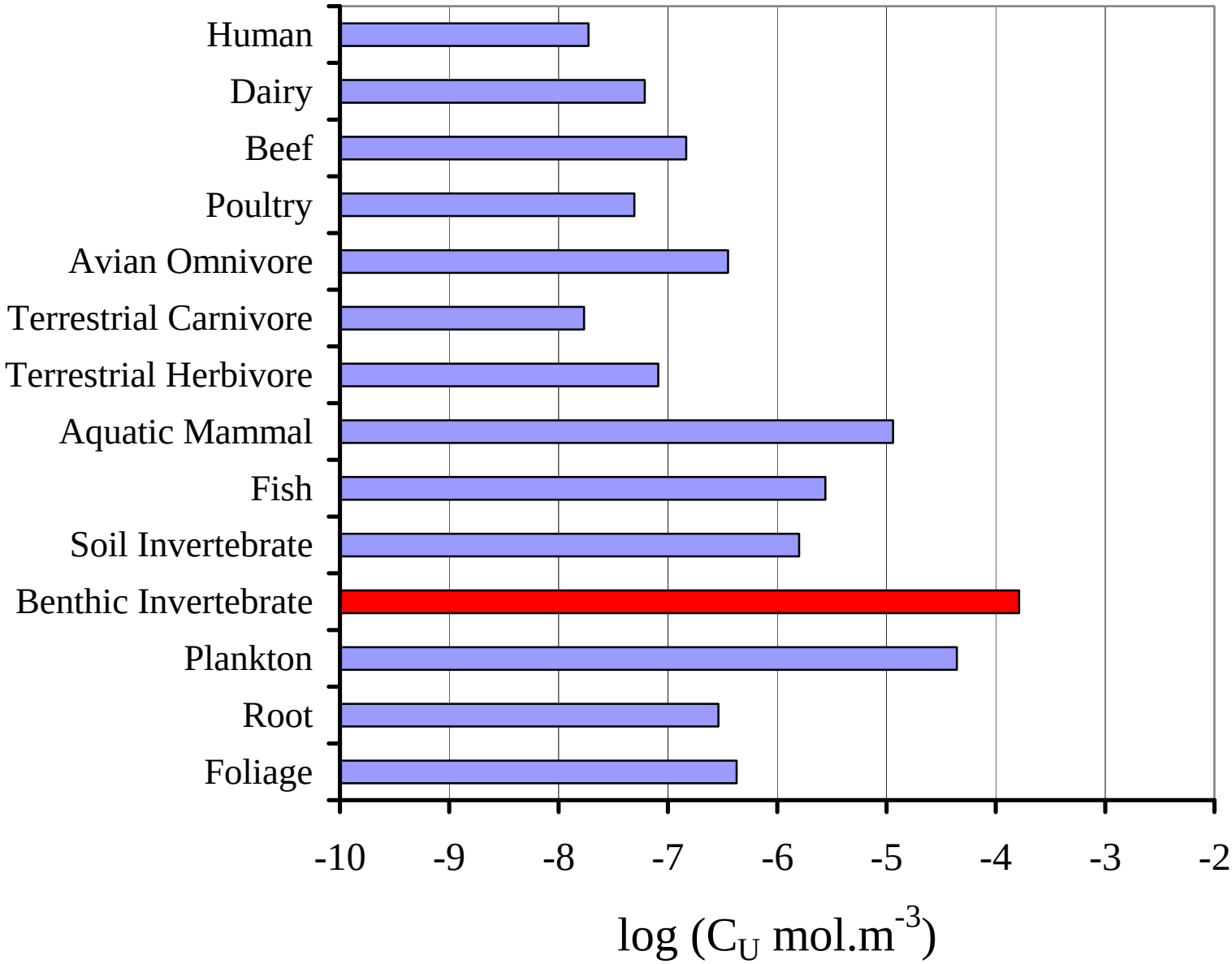
Running the model

- 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)

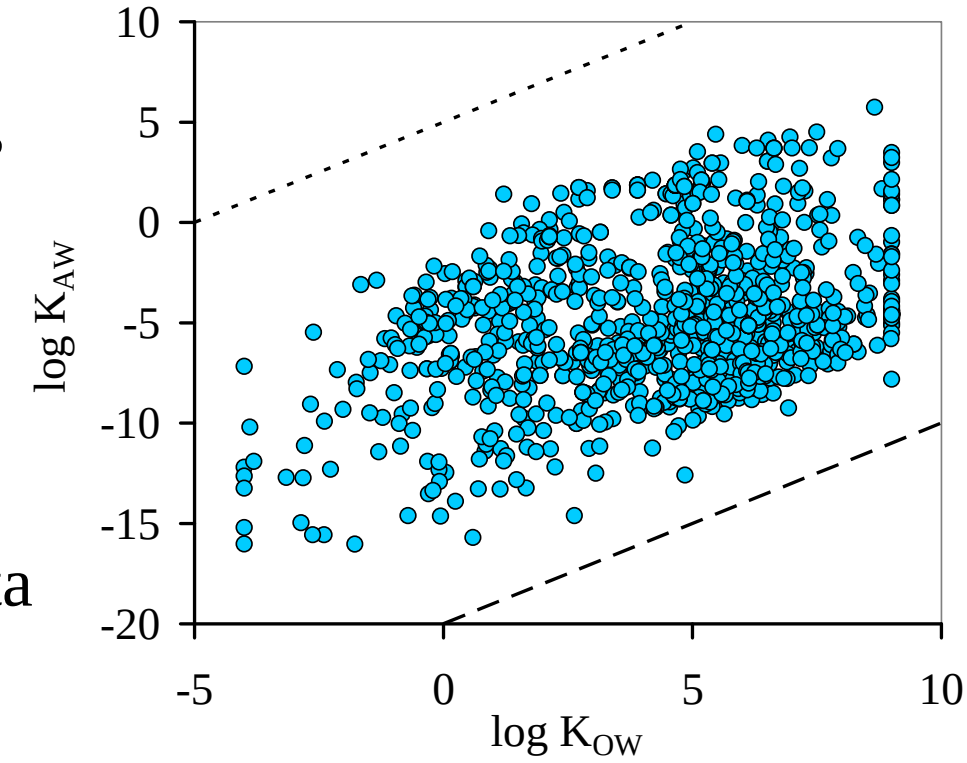


Risk calculations (e.g.)

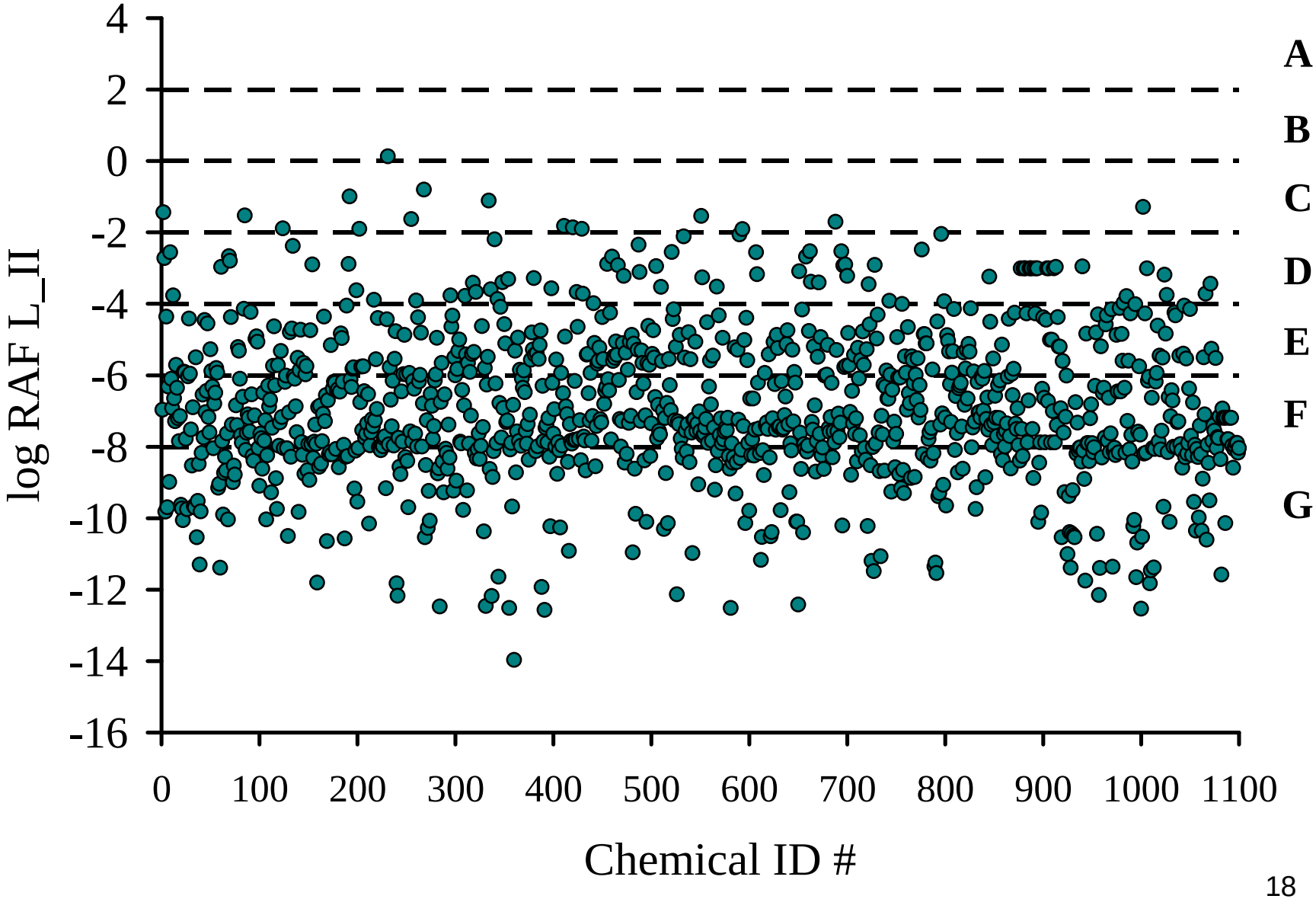
- Unit concentrations in all biota C_U (mol/m^3)
- Hazard quotients for all biota, i.e., HQ = C_U / C_T
- Identify most sensitive receptor, i.e., HQmax
- Back-calculate the 'critical' emission rate
  - i.e., $E_C = E_U$ / HQmax
- Risk Assessment Factor (RAF) = E_A / E_C
  - High RAF — high concern
  - 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 kg/h
- E_A DSL quantity estimates
- Selected effect endpoint
  - C_T
  - DSL acute lethality data
  - Critical body residues



Prioritizing risk: *n* = 1,100



Prioritizing risk

	LII	LIII A,W,S	LIII Air	LIII Water	LIII Soil	*n* = 1,100
RIB	Count	Count	Count	Count	Count	Average frequency
A	0	0	1	0	0	0.00018
B	1	6	10	2	2	0.0038
C	15	62	19	64	17	0.03204
D	79	193	82	197	81	0.11439
E	251	365	256	457	313	0.29719
F	450	439	456	308	457	0.3819
G	309	40	281	77	235	0.1705

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

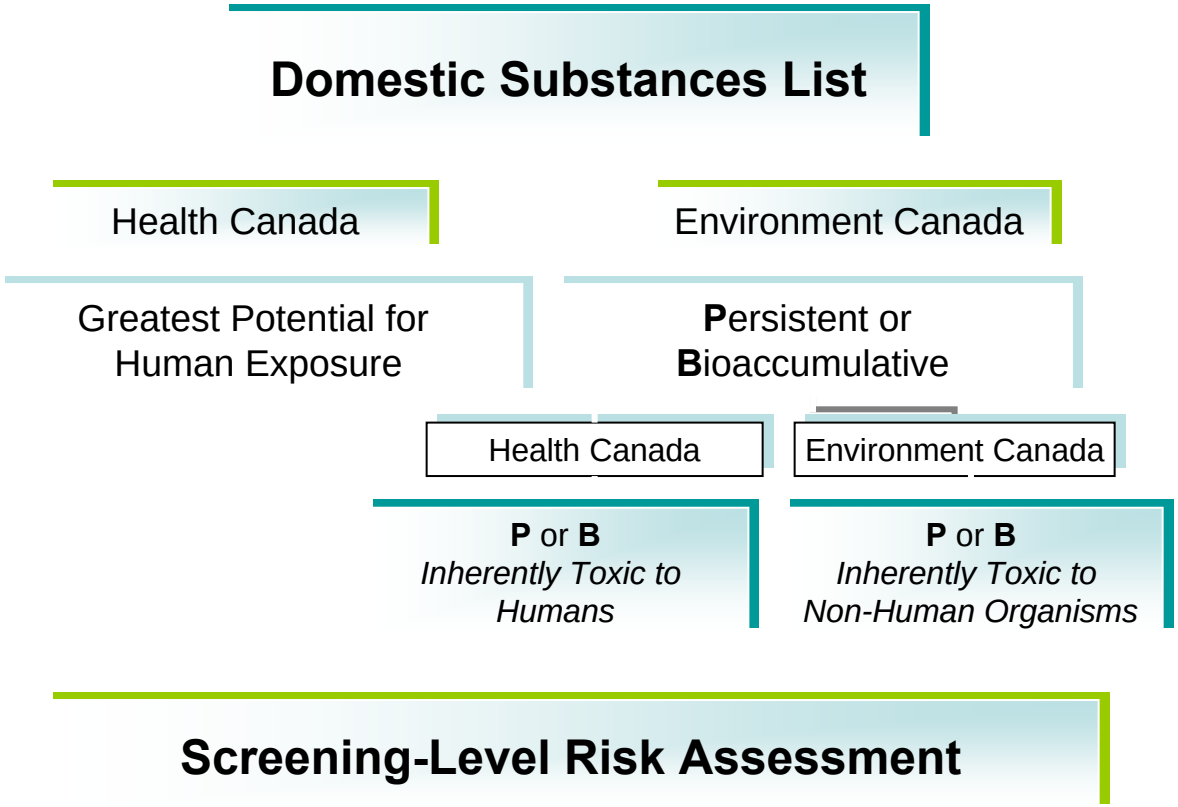
Example of typical “bright line” PBT assessment:

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 $\mathbf{E_A}$; 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:

$RAF = E_A DT$ = 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

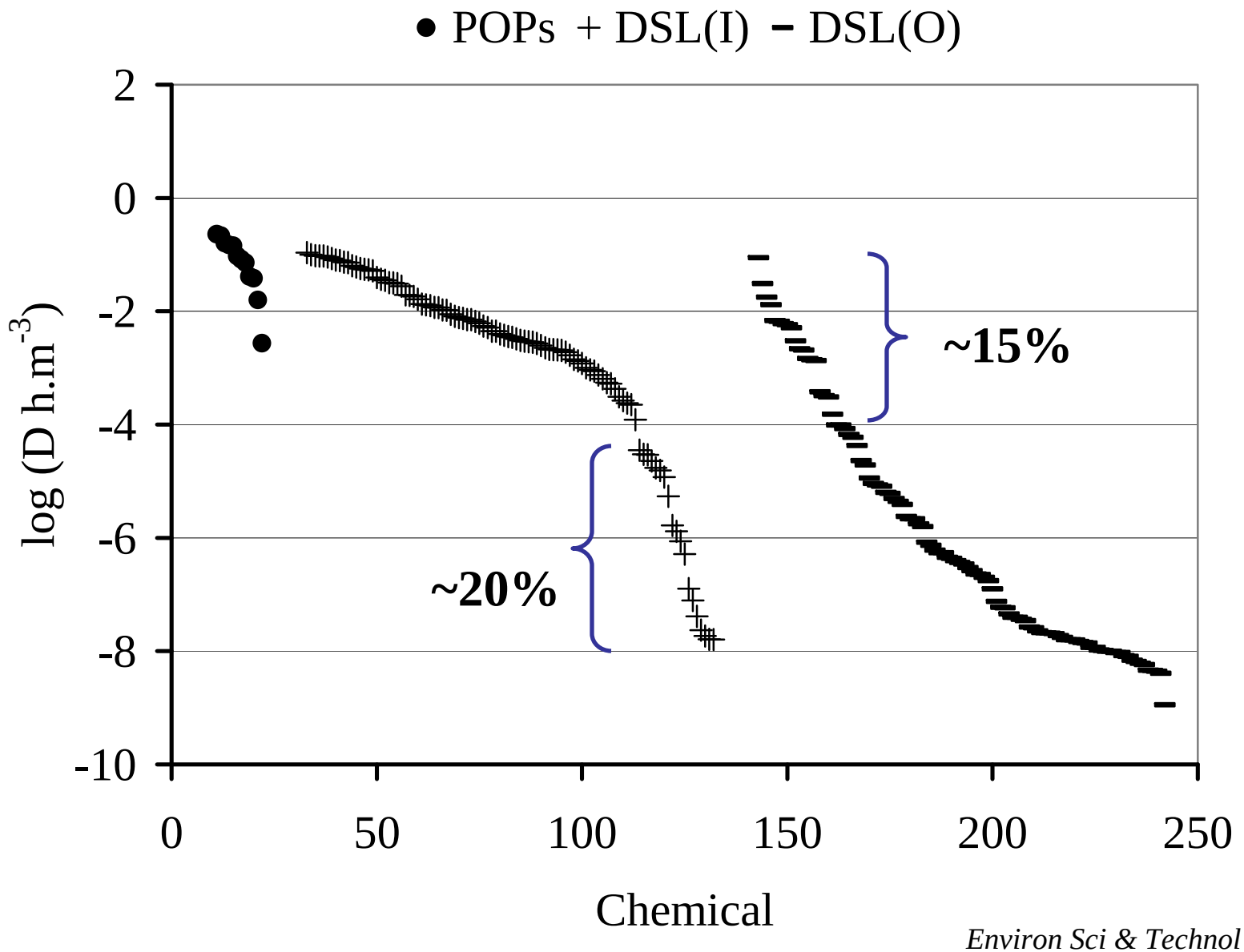
Holistic methods: RAIDAR EAF, HAF and RAF calculations

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)

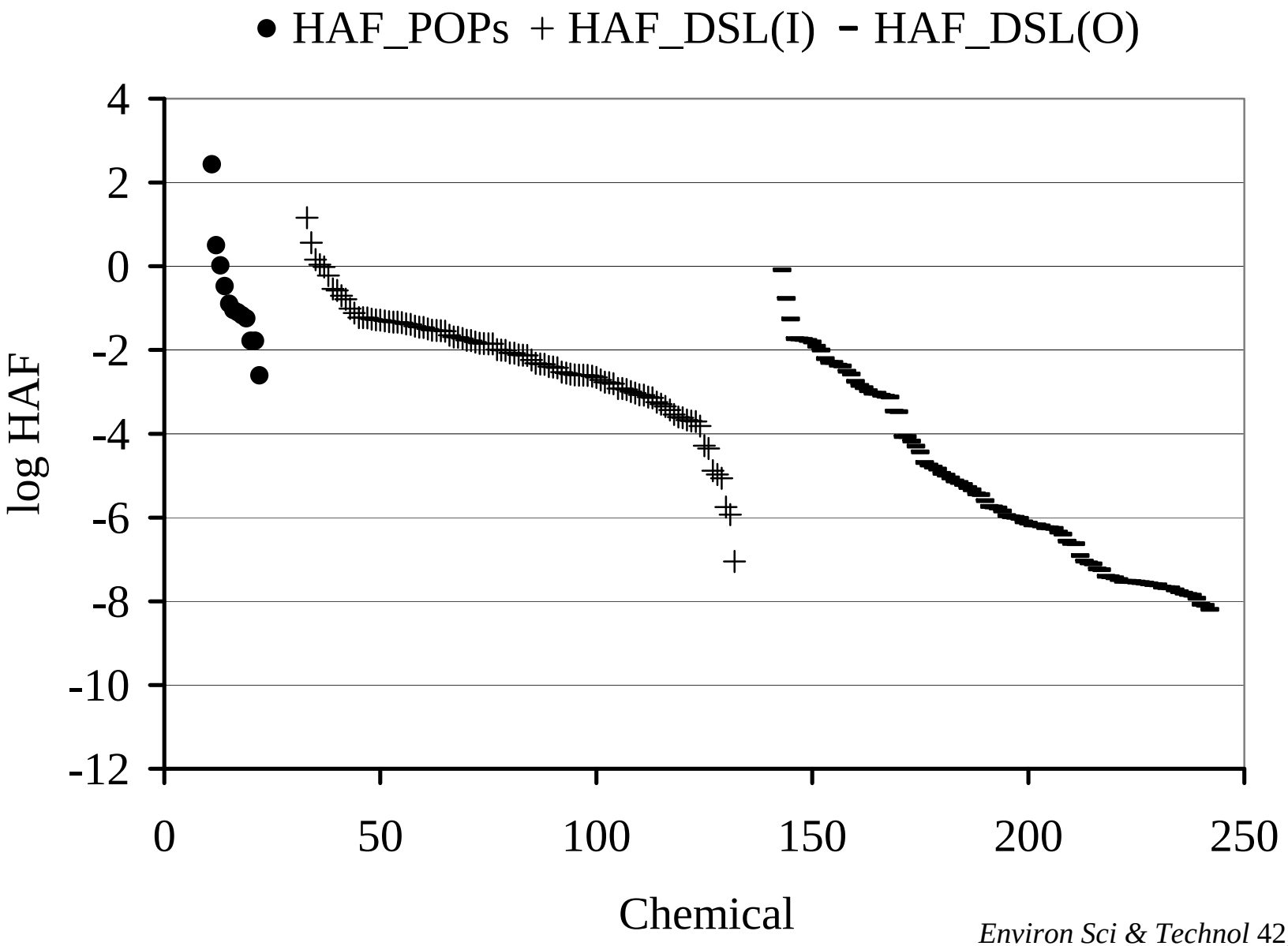
1. Use same basic information available for the categorization for RAIDAR calculations, i.e., "no biotransformation"
2. Include estimates for biotransformation using novel QSAR

Delivery – D; maximum EAF (P,B): all species



Environ Sci & Technol 42, 4648-4654

Hazard (P,B,T)



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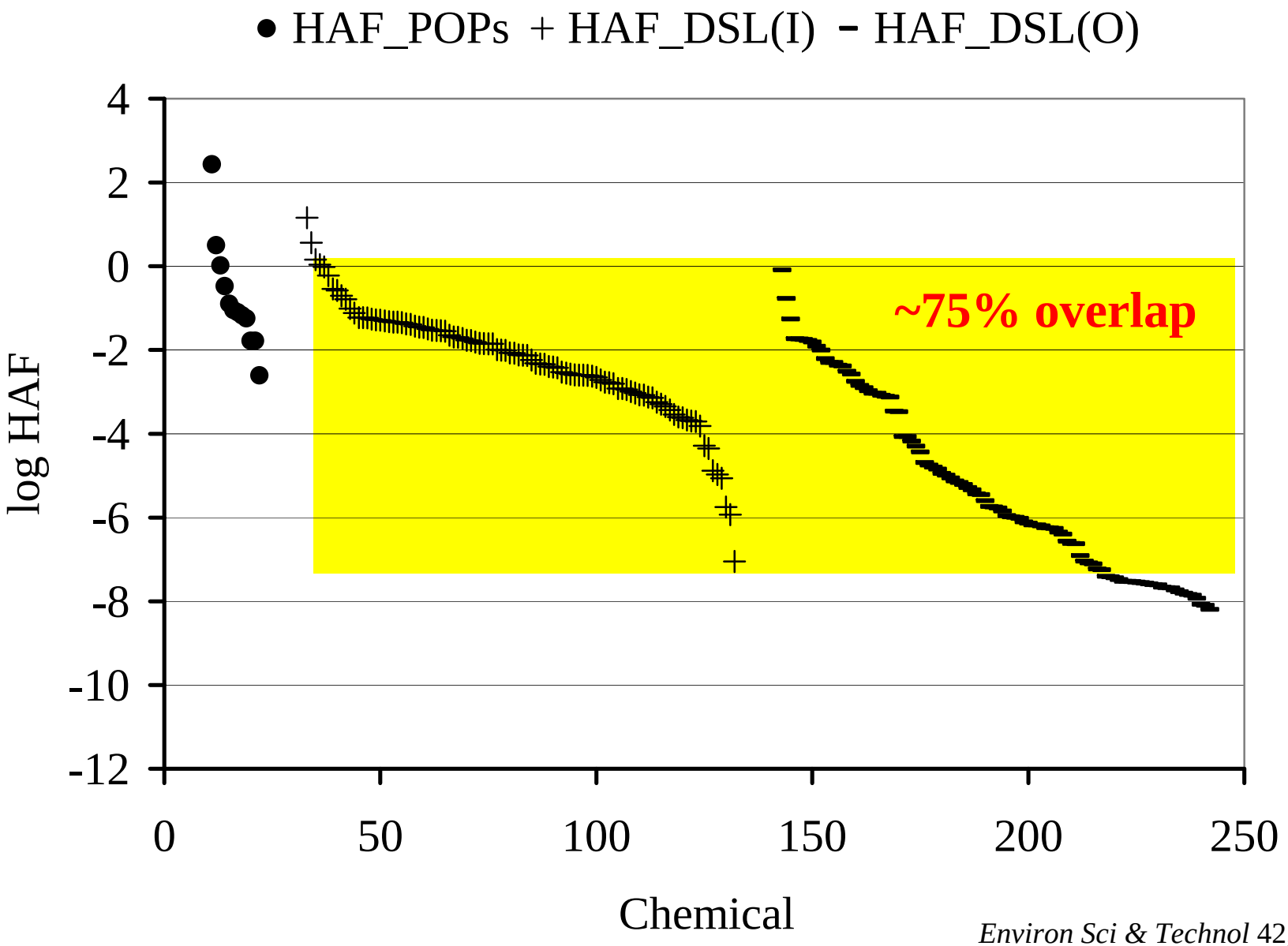
Hazard (P,B,T)



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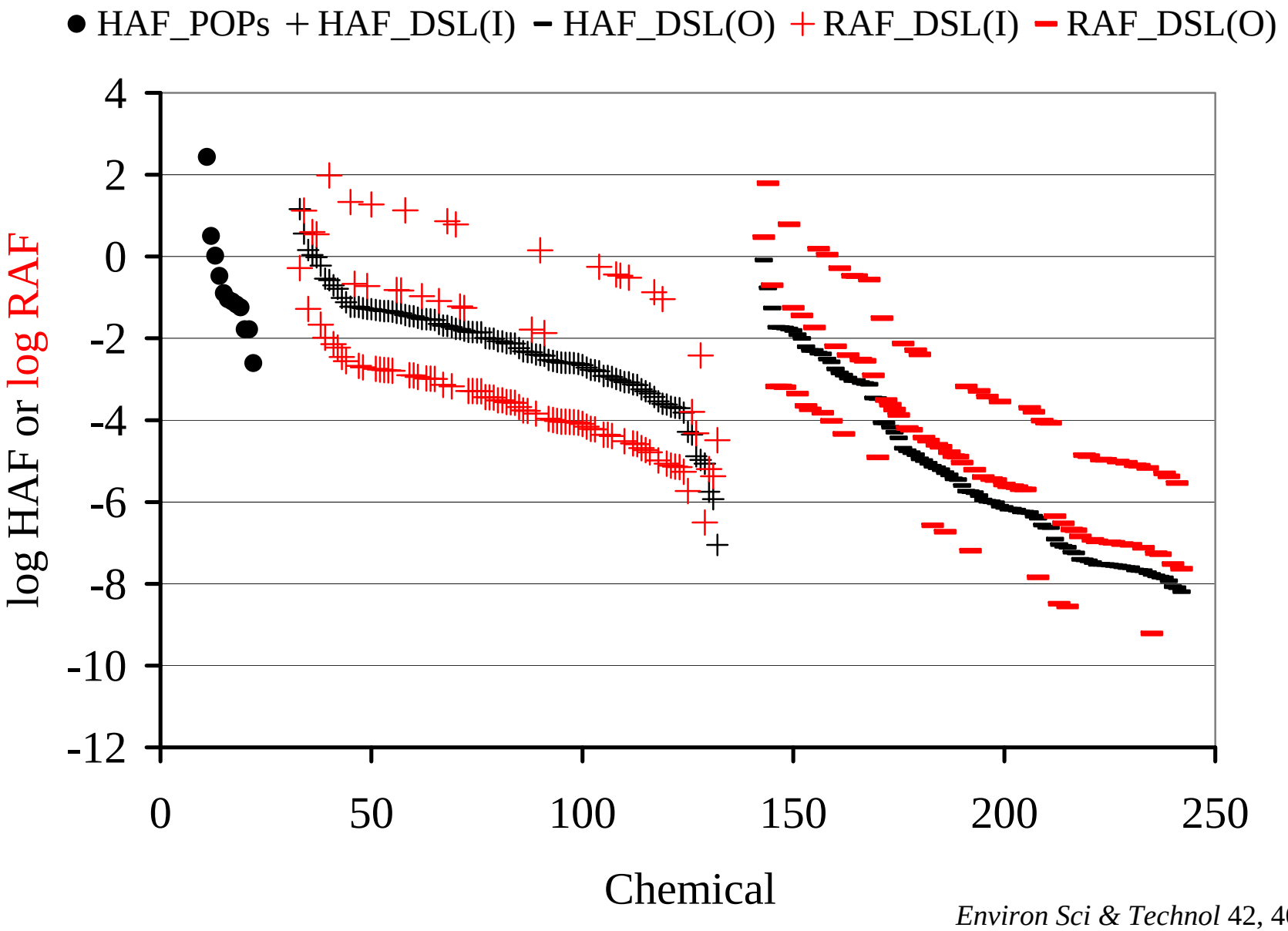
Risk (Q,P,B,T)



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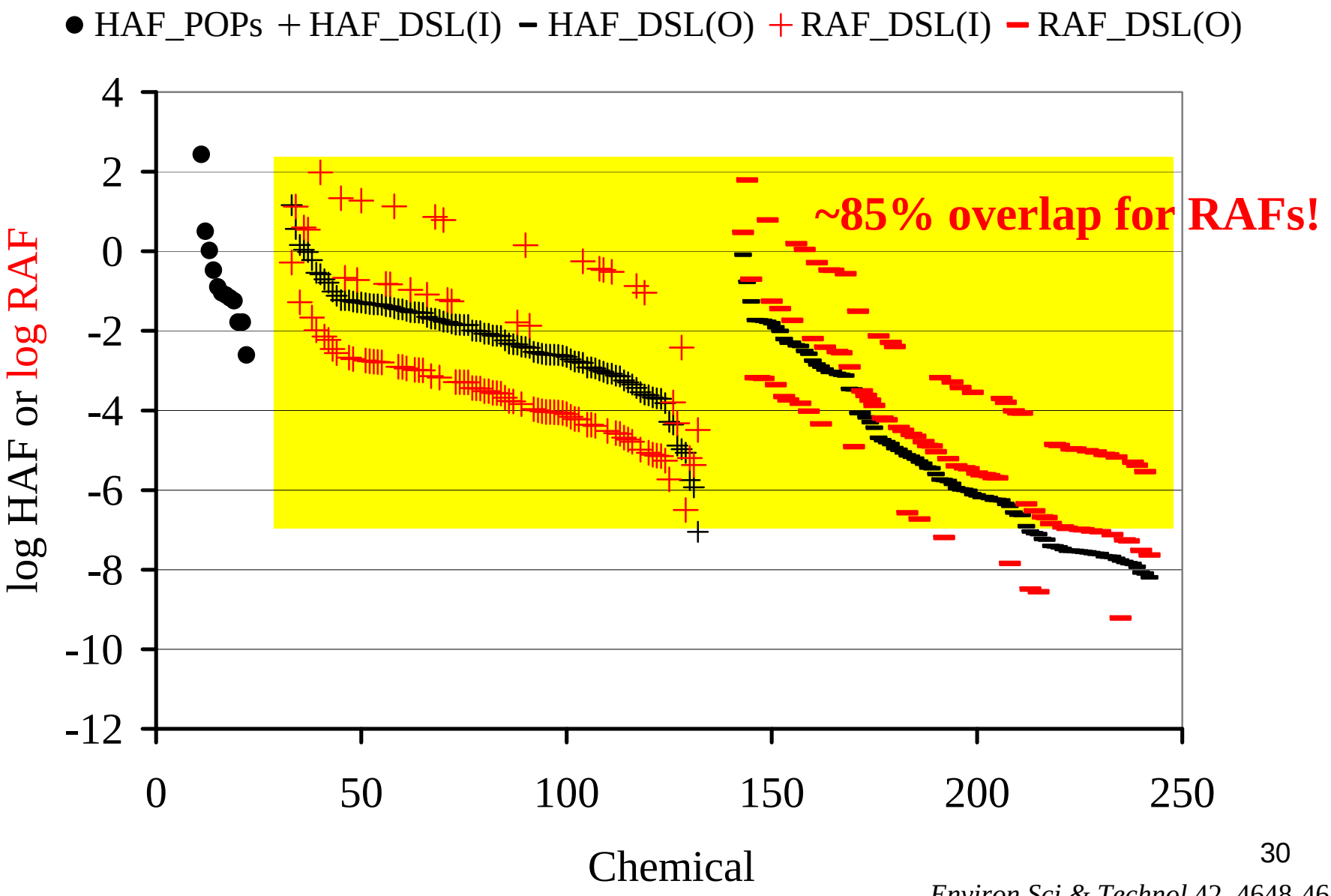
Risk (Q,P,B,T)



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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”

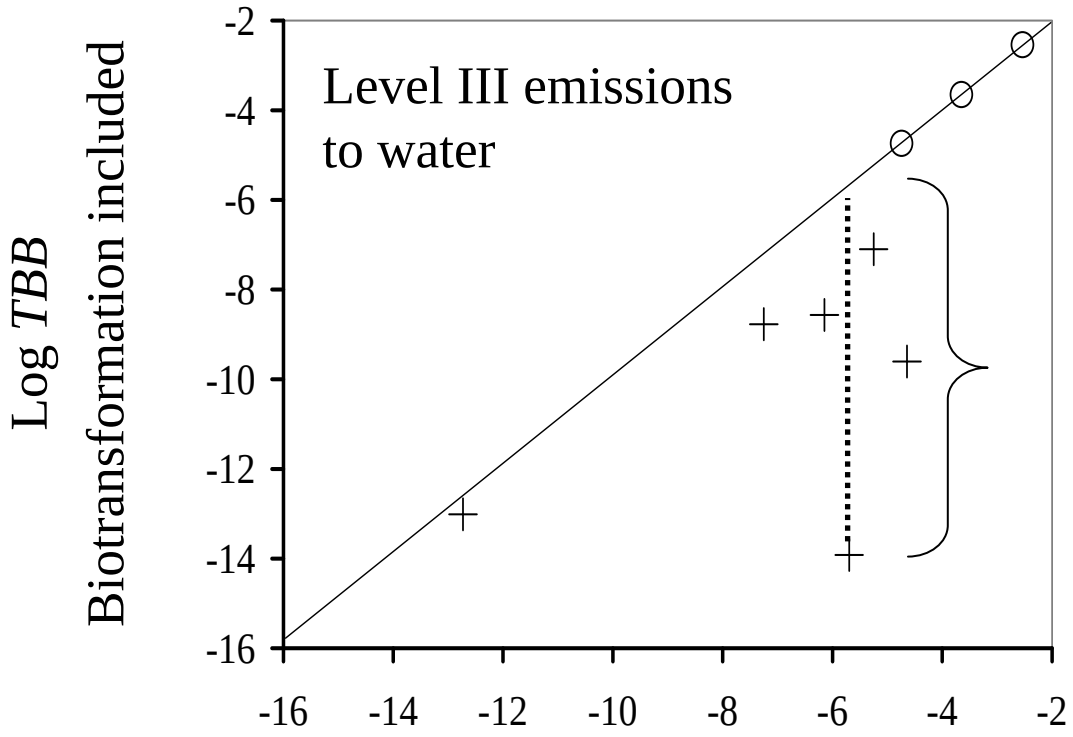
• A QSAR was developed and evaluated to predict primary biotransformation rate constants from chemical structure using in vivo biotransformation rate constant estimates for ~700 chemicals in fish

• U.S. EPA’s EPI Suite Ver. 4.0

Environ Toxicol Chem 28, 1168-1177

Human total body burden (*TBB*) predictions: influence of biotransformation assumptions

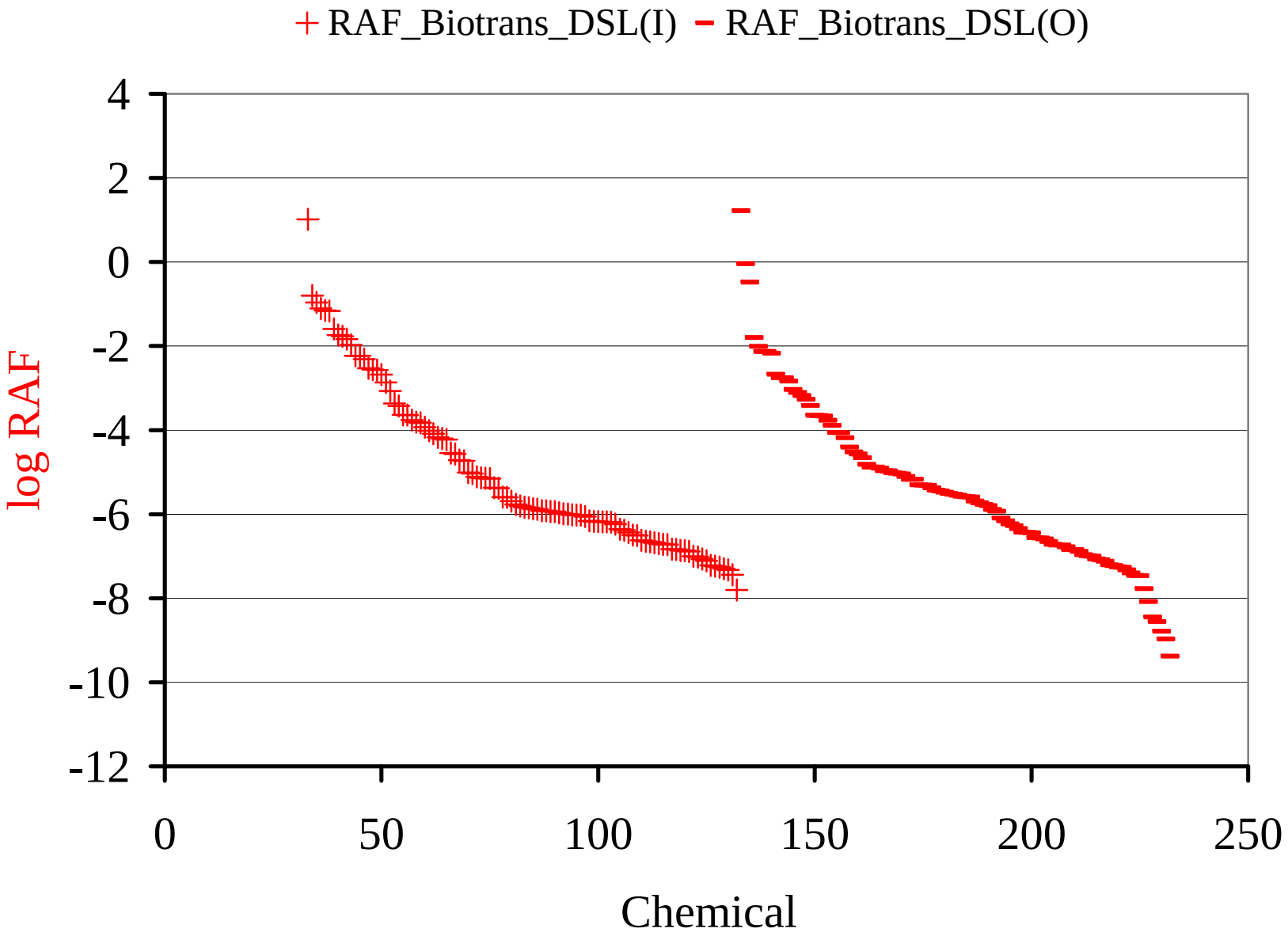
o: POPs; +: non POPs



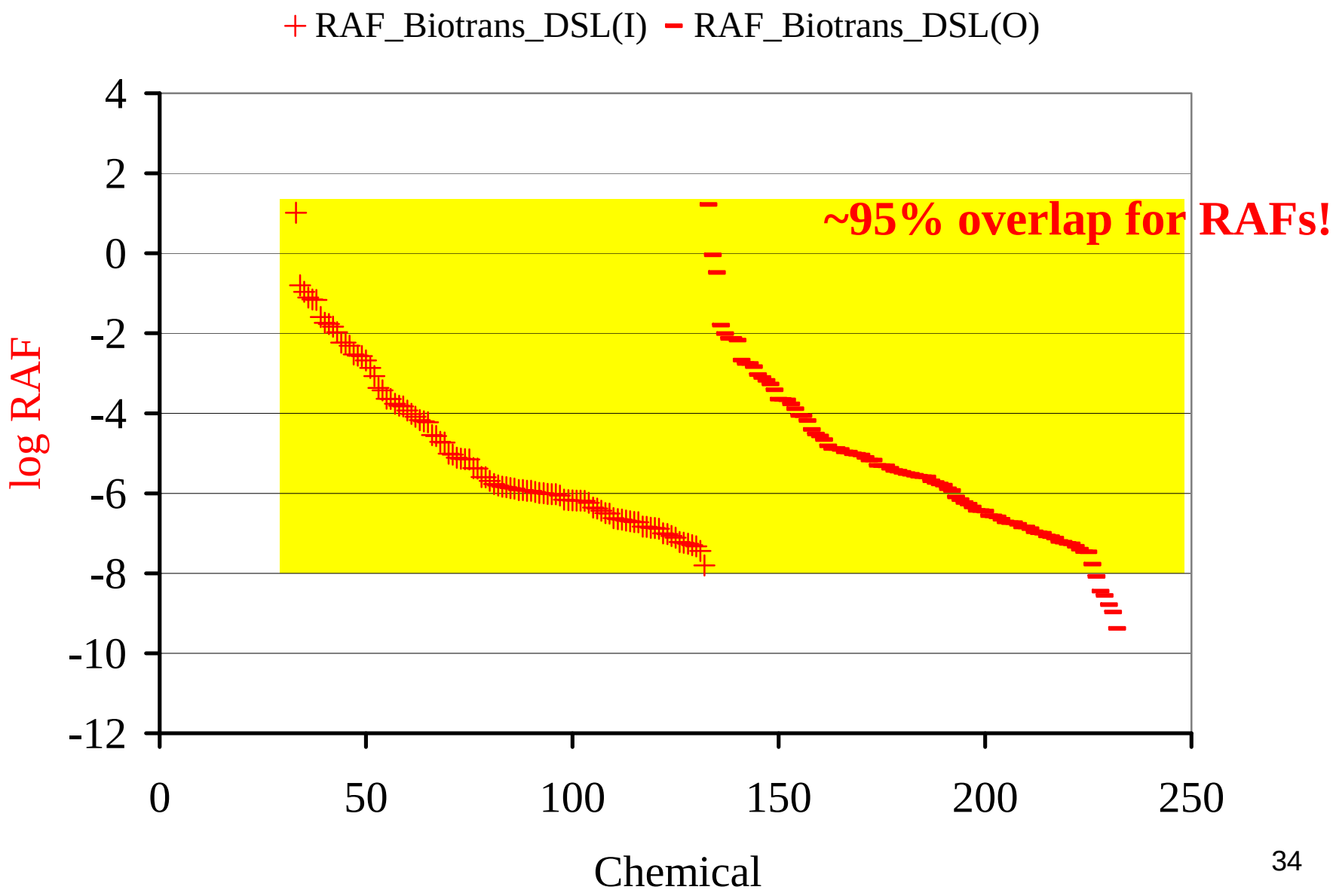
~10^8 difference in *TBB* when estimates included

Environ Toxicol Chem in press

Risk (Q,P,B,T including biotransformation)



Risk (Q,P,B,T including biotransformation)



Priority setting methods summary

Current methods

Category based screening for priority assessment

Screening pass/fail values against cut-off criteria for P, B, T and Q determines further assessment outcomes, e.g., BCF ≥5,000 is “B”; BCF <5,000 is “not B”

Multiple binary assessments require judgment, e.g., “P and T; not B” or “T; not P and B”

Reliability of category criteria determines further assessment outcomes, e.g., B criteria do not exist for air-breathing organisms

Type I and II error potential high in screening stages, e.g., BCF = 5,100 vs. 4,900; or $t_{1/2}$ air = 2.1 d vs. 1.9 d

Uncertainty not considered until risk assessment stage

Proposed holistic methods

Holistic strategy for exposure, hazard, and risk

No bright line criteria

No judgment required for multiple binary outcomes

Direct chemical comparisons for exposure, hazard and risk

Reliability of category criteria not a factor

Uncertainty can be included for hazard, exposure, and risk

Provides guidance for monitoring and green chemistry

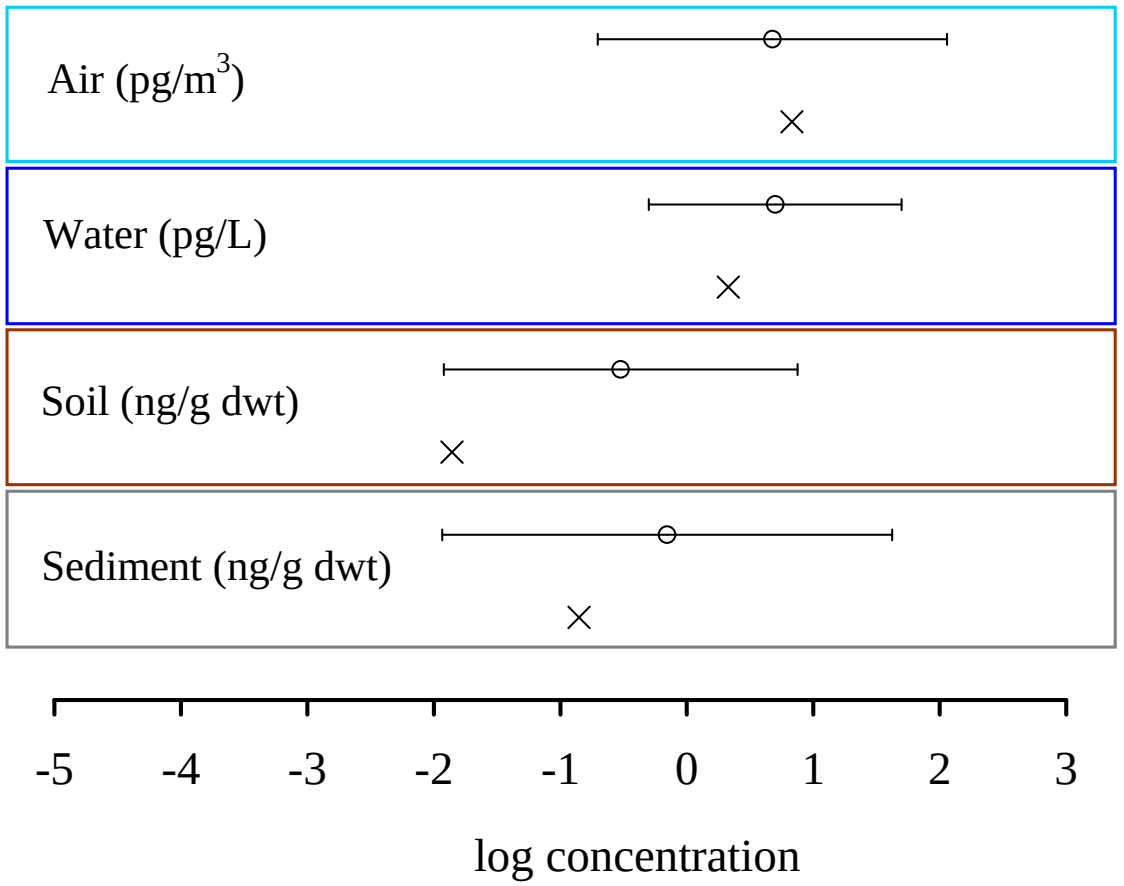
Implications

- 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

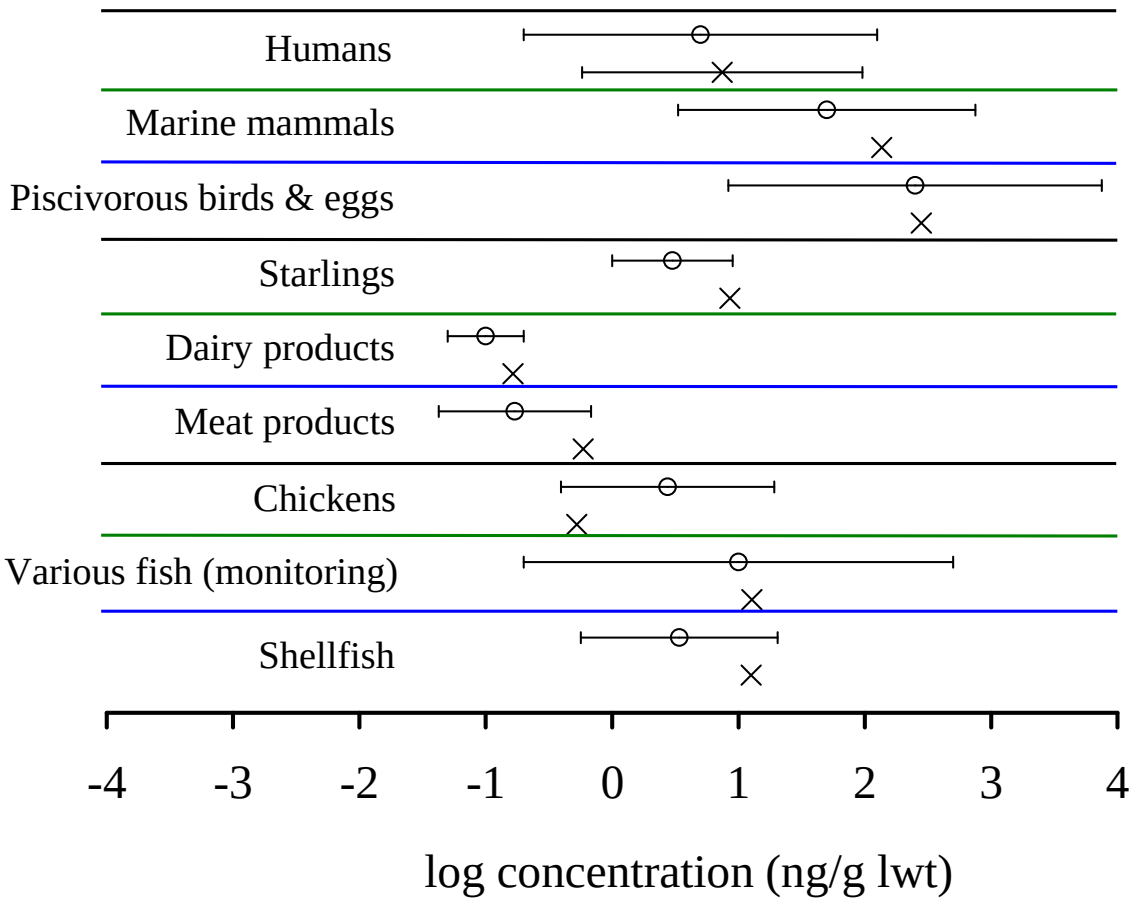
- Difficult to “validate” evaluative models, e.g.,
  - Monitoring data are limited
  - RAIDAR is not “site specific”, “representative conditions”
  - Spatial and temporal issues (heterogeneity, steady-state)
- Case study for commercial pentabromodiphenyl ether (PBDE-99)
- Determine realistic “actual” 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)



Integ Environ Assess Manag on-line June 22, 2009

PBDE 99: monitoring data (o) / model (x)



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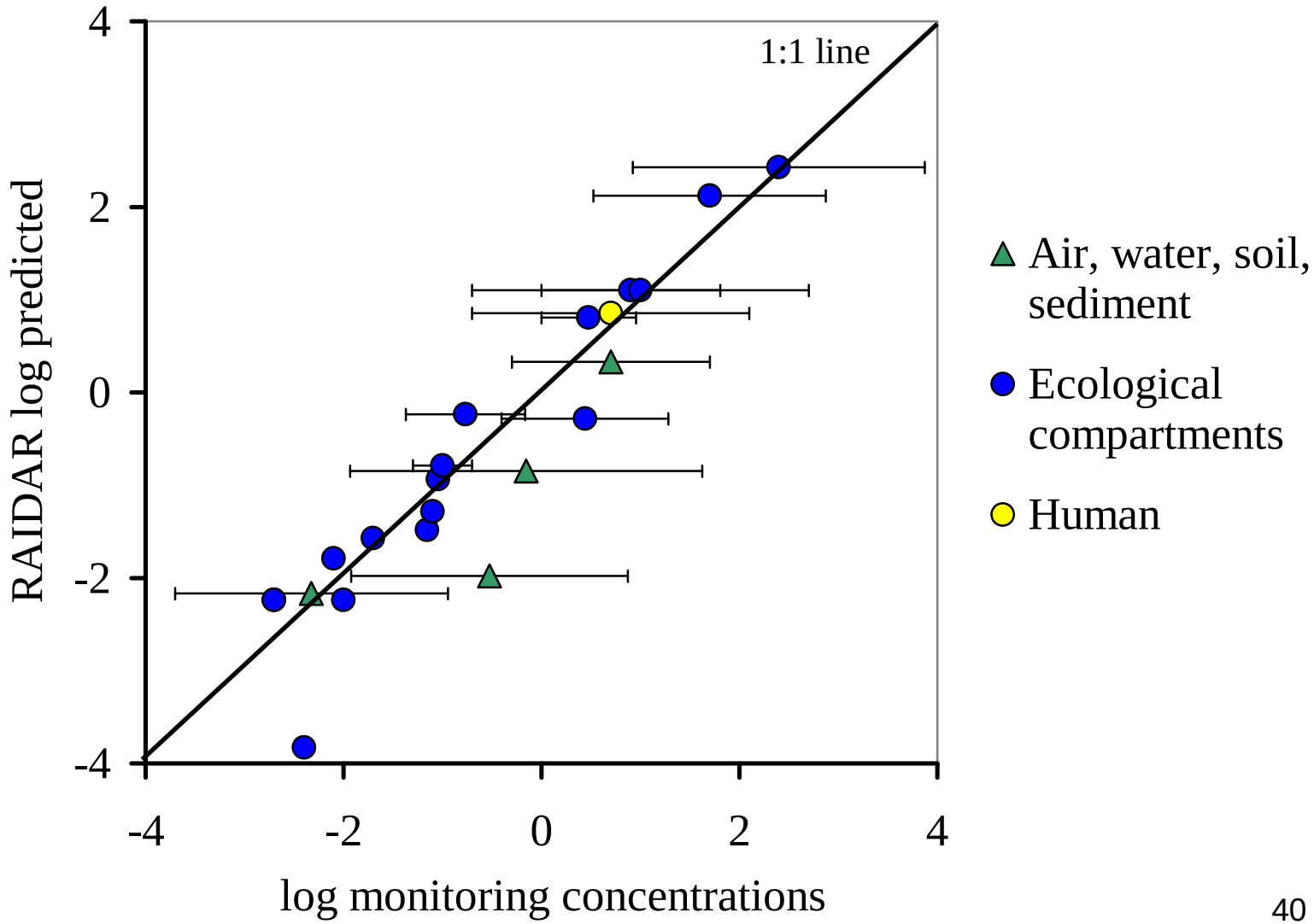
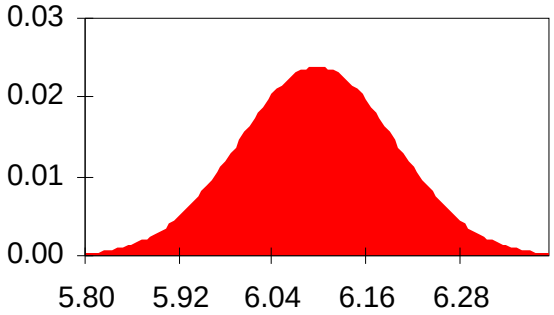
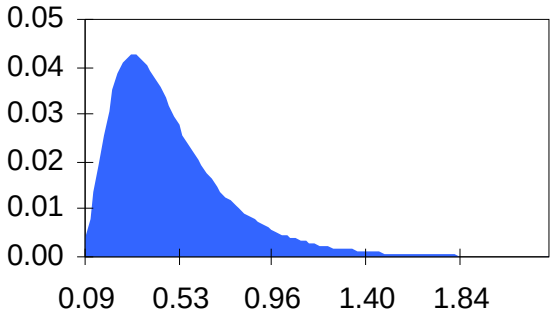
PBDE-99 model and monitoring data



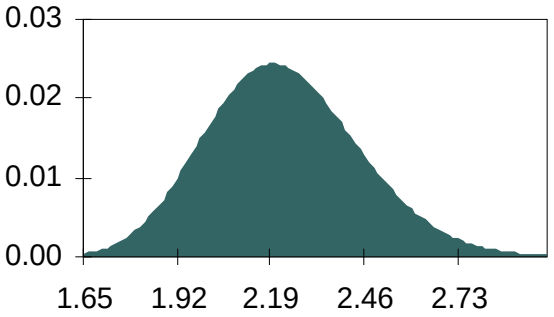
Including uncertainty in predictions



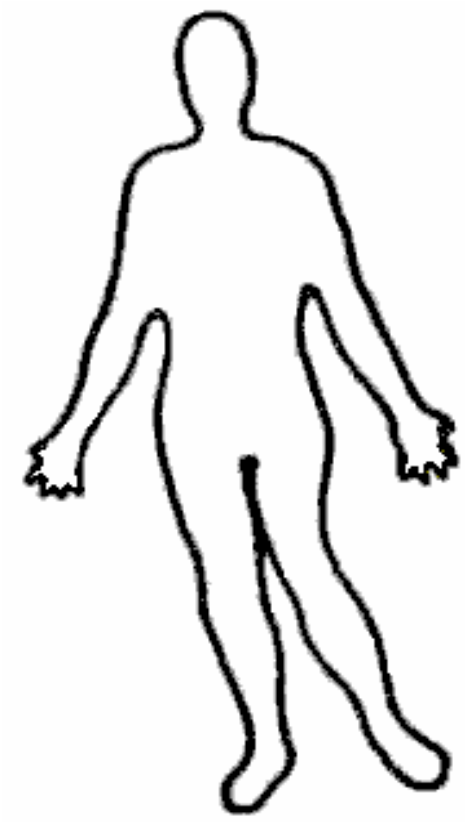
log K_{OW}



Biotransformation



log half-life water (days)



Propagation of uncertainty in exposure and risk assessments

What dictates uncertainty in the RAF ?

$$RAF = E_A \cdot \frac{C_U}{E_U} \cdot \frac{1}{C_T}$$

Quantity emitted

RAIDAR estimate of environmental Delivery

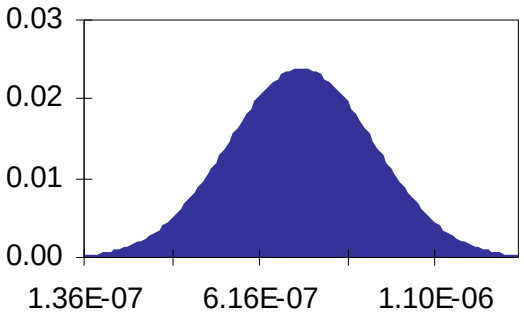
Toxicity of most sensitive receptor

- 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”)

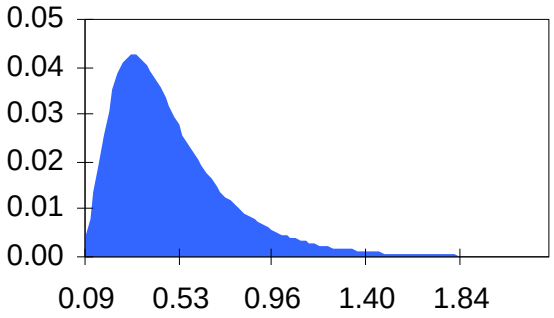
Prioritizing uncertainty:

Which are the most sensitive and uncertain parameters?

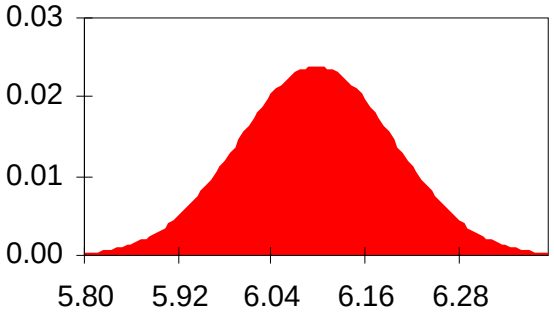
What research effort will get the most “bang for the buck”?



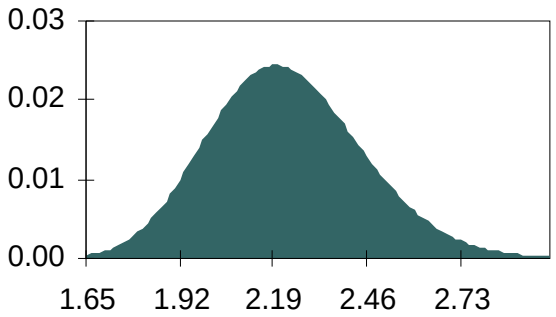
VP (Pa)



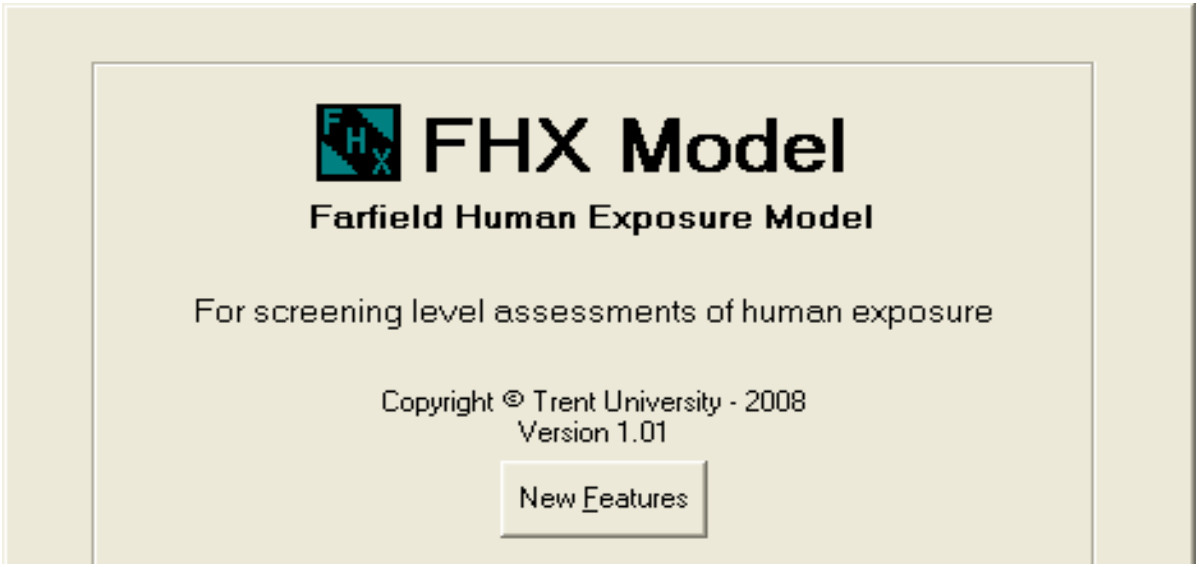
k_M fish d^{-1}



log K_{OW}



log half-life water (days)


FHX Model
Farfield Human Exposure Model
For screening level assessments of human exposure
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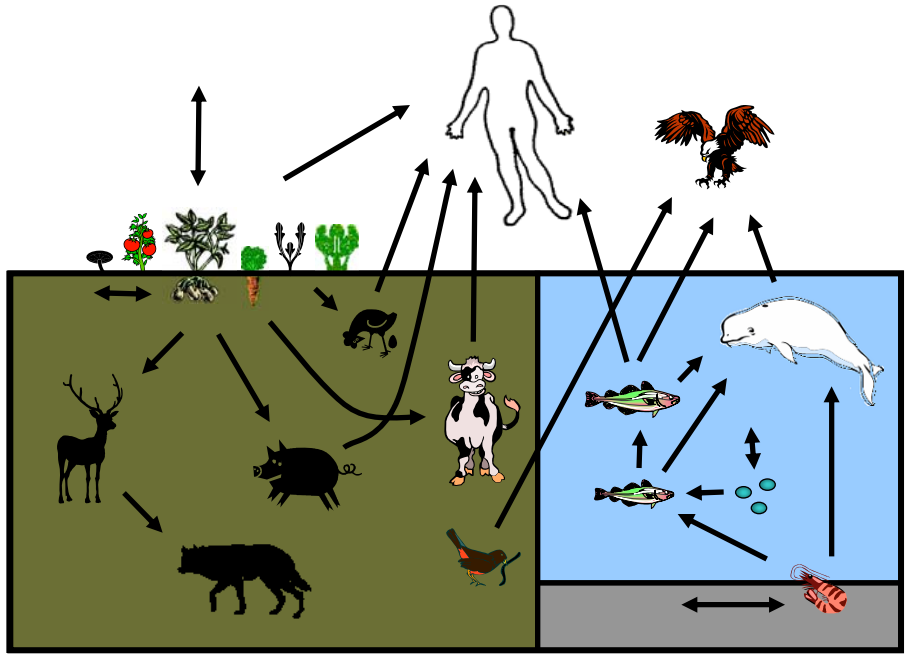
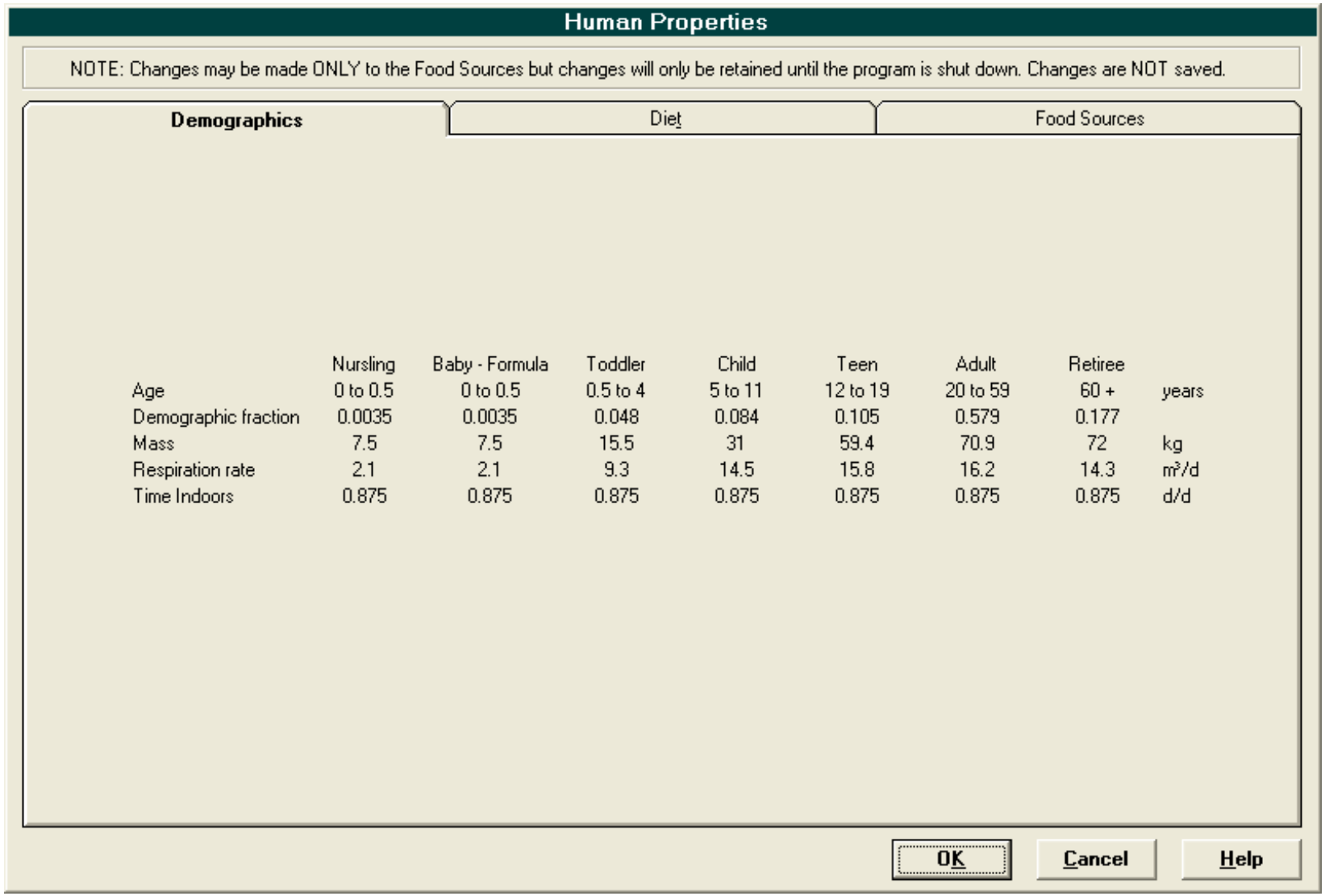
Version 1.01
New Features



Health Canada Age Classes



	Nursling	Baby - Formula	Toddler	Child	Teen	Adult	Retiree	
Age	0 to 0.5	0 to 0.5	0.5 to 4	5 to 11	12 to 19	20 to 59	60 +	years
Demographic fraction	0.0035	0.0035	0.048	0.084	0.105	0.579	0.177	
Mass	7.5	7.5	15.5	31	59.4	70.9	72	kg
Respiration rate	2.1	2.1	9.3	14.5	15.8	16.2	14.3	m^3/d
Time Indoors	0.875	0.875	0.875	0.875	0.875	0.875	0.875	d/d

Health Canada Age Class Specific Intake

Human Exposure

CAS: 71432 **Benzene (BZ)**

sample environment

Overview | Details

Intake Rate µg/d

	Nursling	Baby - Formula	Toddler	Child	Teen	Adult	Retiree
Foods	4.26E-05	4.26E-05	5.57E-05	7.25E-05	8.44E-05	7.17E-05	6.04E-05
Liquids	3.22E-07	7.50E-07	8.65E-07	1.33E-06	1.60E-06	2.33E-06	2.25E-06
Soil & Dust	7.15E-11	7.15E-11	2.38E-10	1.55E-10	7.15E-11	7.15E-11	7.15E-11
Air	1.38E-03	1.38E-03	6.09E-03	9.49E-03	0.0103	0.0106	9.36E-03
Total	1.42E-03	1.42E-03	6.15E-03	9.57E-03	0.0104	0.0107	9.43E-03

Intake Fraction

	Nursling	Baby - Formula	Toddler	Child	Teen	Adult	Retiree
Individual	5.91E-14	5.91E-14	2.56E-13	3.99E-13	4.35E-13	4.45E-13	3.93E-13
Population	6.20E-09	6.21E-09	3.69E-07	1.00E-06	1.37E-06	7.73E-06	2.09E-06

Total 1.26E-05

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

Thank you for your interest and attention!

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