The Bioaccumulation Assessment Tool (BAT)

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ECHA PBT EG

September 25, 2018

Presentation Overview

- Rationale & Objectives
- The BAT WOE Approach
  - Relevance
  - Reliability
  - Strength
- BAT Concepts
- Examples of Input and Output

Project Overview

Timeline:

Initiated: Fall 2016

Completed: September 2018

Available: www.arnotresearch.com & www.cefic-lri.org

BAT Research Team Members:

- Jon Arnot, PhD
- James Armitage, PhD
- Liisa Toose, MSc
- Michelle Embry, PhD
- Karen Foster, PhD
- Lauren Hughes, MSc

Stakeholder Involvement:

BAT Advisory Team (BAT-AT) providing comments and suggestions

- Johanna Peltola-Thies and others (ECHA)
- Caren Rauert (UBA)
- Ian Doyle (UK Environment Agency)
- Naoki Hashizume (CERI)
- Yoshiyuki Inoue (CERI)
- Mark Bonnell (ECCC)
- John Nichols (EPA)
- Karen Eisenreich (EPA)
- David Tobias (EPA)
- Kent Woodburn (Dow)
- Sami Belkhiria (Dow)
- Sylvia Jacobi (Albemarle Europe sprl)
- Florian Schmidt (BASF)
- Marie-Helene Enrici (Solvay)

Rationale

Various…

1. **Regulatory programs**:
   - REACH, TSCA, CEPA, CSCL, Stockholm Convention
2. **Metrics:**
   - Kow, lab BCF, lab BMF, field BMF, field BAF, field TMF, etc
3. **Criteria:**
   - 1, 500, 1000, 2000, 5000

- Weight of Evidence (WOE) approach suggested, e.g., REACH Annex XIII
- But **NO** organizational framework or defined implementation strategy for assessments -> “challenging”

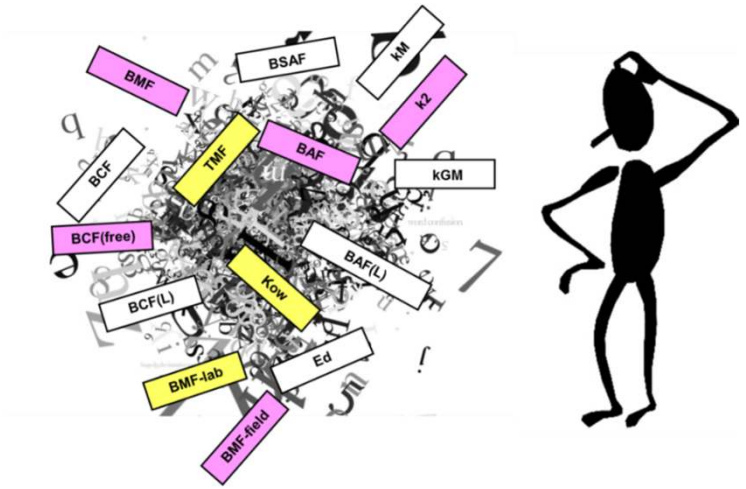
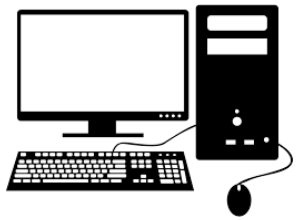


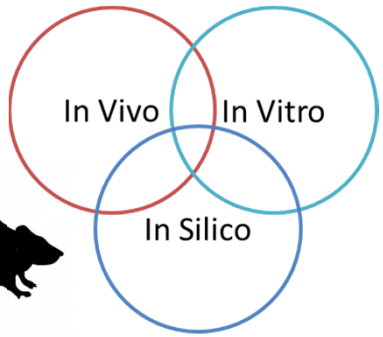
Fig from Gobas

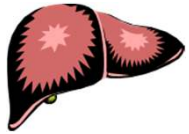
General Project Objectives

Develop a user-friendly spreadsheet tool that can be used to:

- **collect**, **generate, evaluate** and **integrate** various lines of evidence (LOE) relevant to B-assessment (i.e., TK, ADME data streams)
- provide **consistent** and **transparent** results by means of a quantitative weight of evidence (QWOE) approach for aquatic and terrestrial B assessment
- **inform** B-assessment decision-making
- guide **testing strategies**



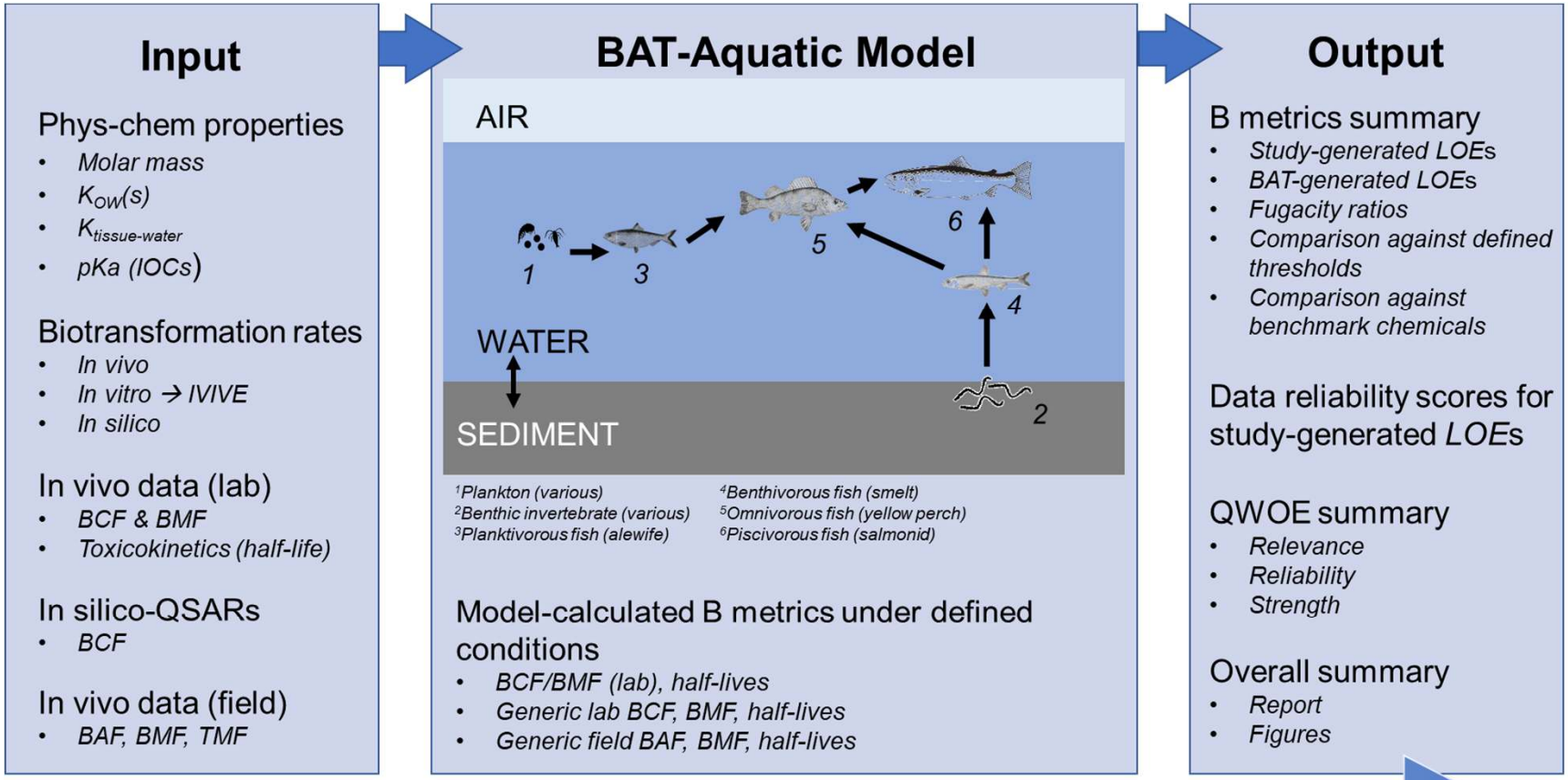




BAT QWOE

- Lines of Evidence (LOE)
  - In Vivo: BCF, lab & field BMF, BAF, TMF
  - In Vitro biotransformation → BCF, BMF, BAF
  - In Silico biotransformation → BCF, BMF, BAF & BCF-QSARs
- Relevance (score)
  - B metrics & source, e.g., lab BCF, field BMF, in silico BCF
- Reliability (score)
  - Data Evaluation Templates (DETs) based on standardized testing guidance → errors/uncertainty in LOE data source
- Strength (score)
  - Summary of LOEs and classifications (“nB”, “B”, “vB”)

BAT Concepts - Aquatic



BAT Concepts - Terrestrial

Input

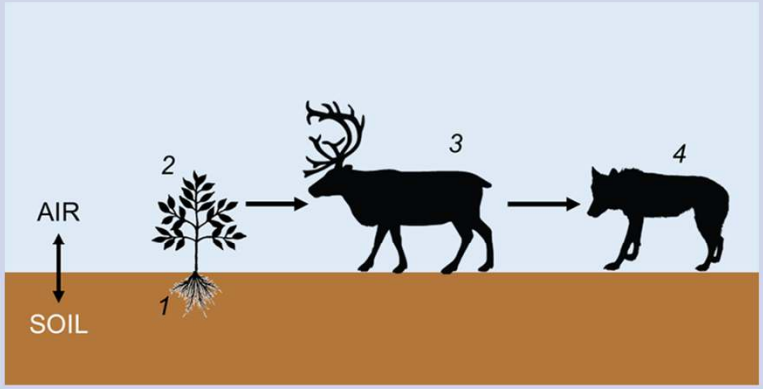
Phys-chem properties
- *Molar mass*
- *K_{OW}(s), K_{OA}(s)*
- *$K_{tissue\text{-}water}$*
- *pKa (IOCs)*

Biotransformation rates
- *In vivo*
- *In vitro → IVIVE*
- *In silico*

In vivo data (lab)
- *BMF*
- *Toxicokinetics (half-life)*

In vivo data (field)
- *BMF, TMF*

BAT-Terrestrial Model



[1]Root vegetation (various)
[2]Foliage vegetation (various)
[3]Terrestrial herbivore (caribou)
[4]Terrestrial carnivore (wolf)

Model-calculated B metrics under defined conditions
- *BCF/BMF (lab), half-lives*
- *Generic lab BCF, BMF, half-lives*
- *Generic field BAF, BMF, half-lives*

Output

B metrics summary
- *Study-generated LOEs*
- *BAT-generated LOEs*
- *Fugacity ratios*
- *Comparison against defined thresholds*
- *Comparison against benchmark chemicals*

Data reliability scores for study-generated *LOEs*

QWOE summary
- *Relevance*
- *Reliability*
- *Strength*

Overall summary
- *Report*
- *Figures*

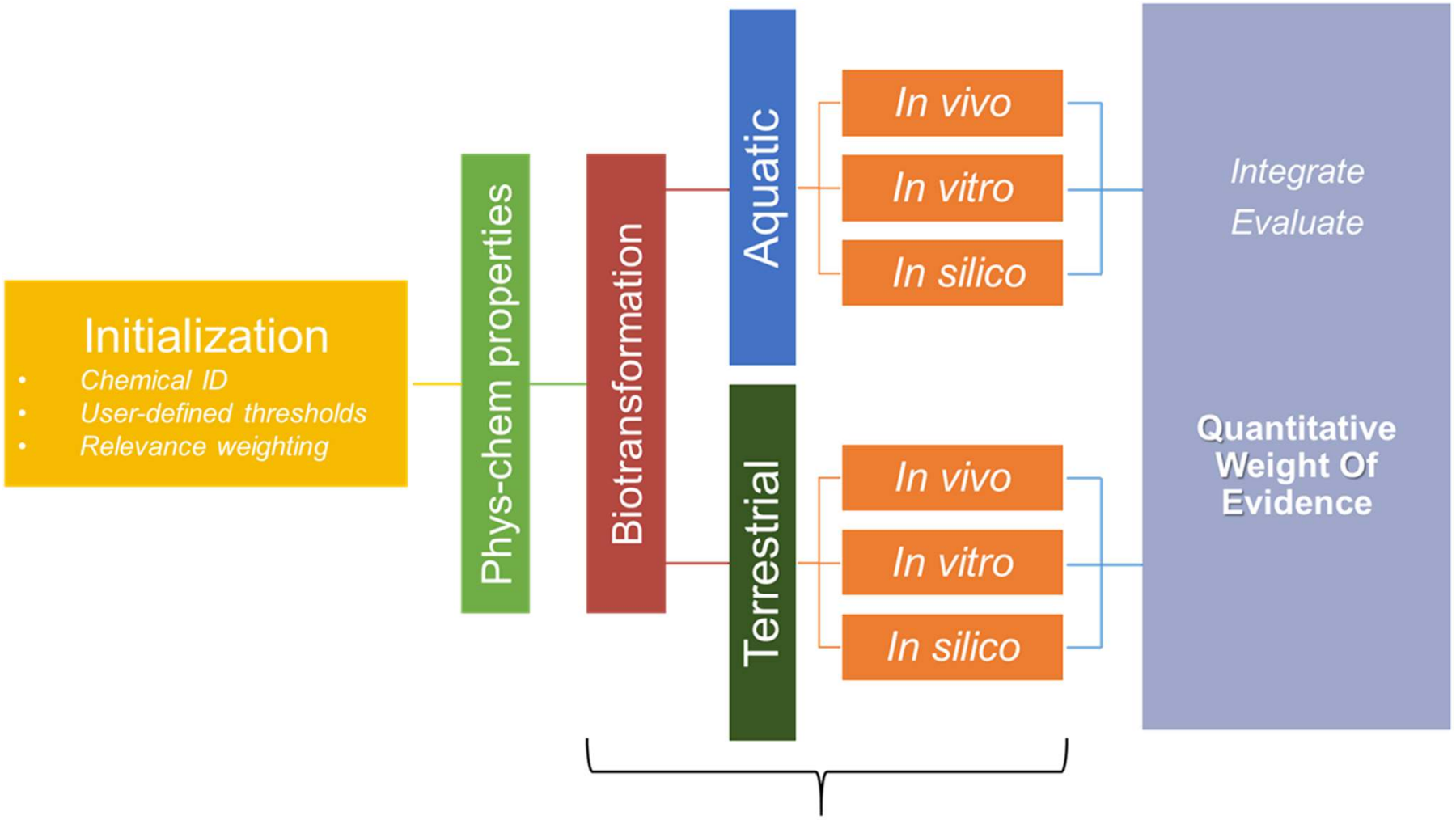
Collects LOE → **Generates LOE** → **Evaluates LOE** → **Integrates LOE**

B metrics

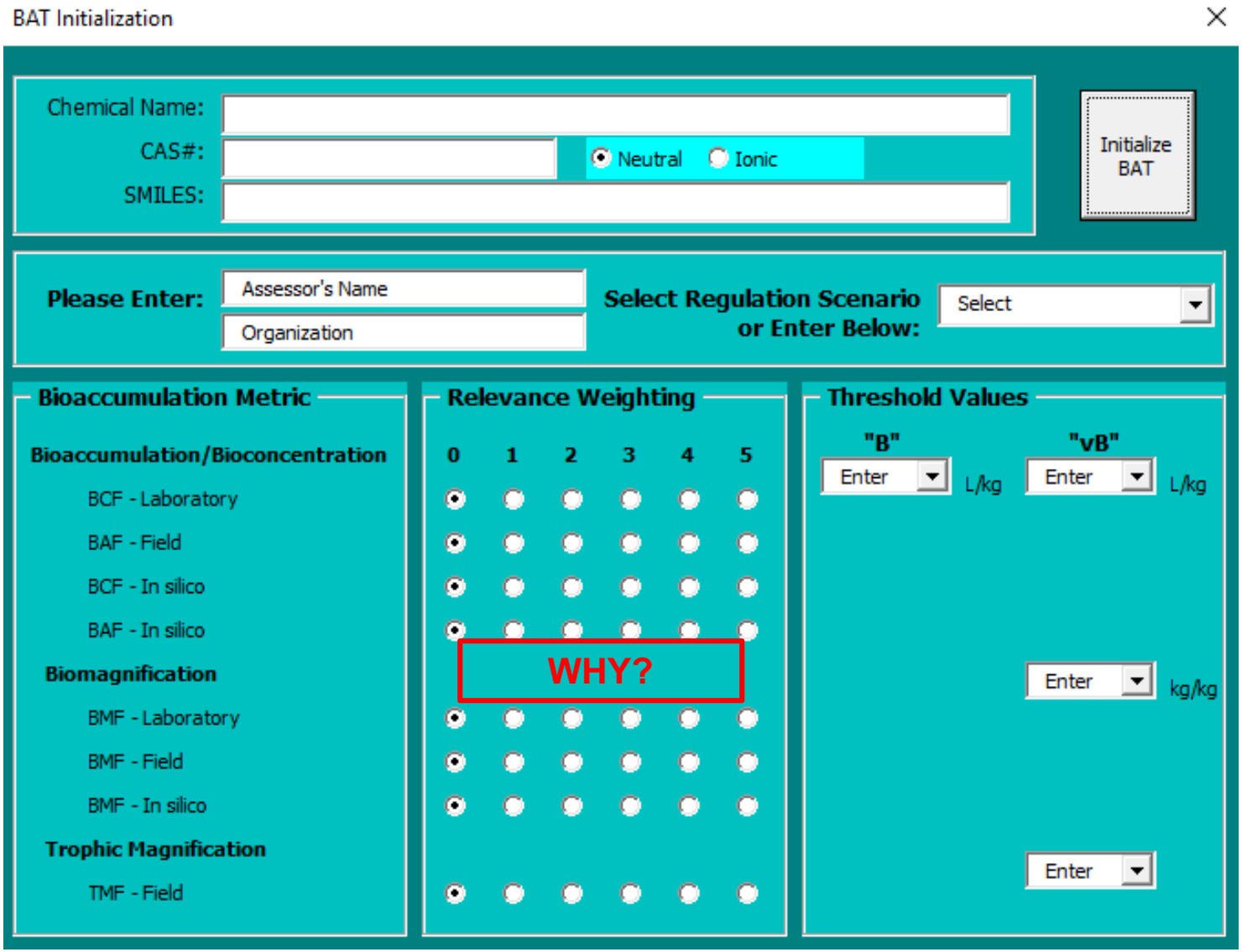
Data Evaluation Templates (DETs)

QWOE

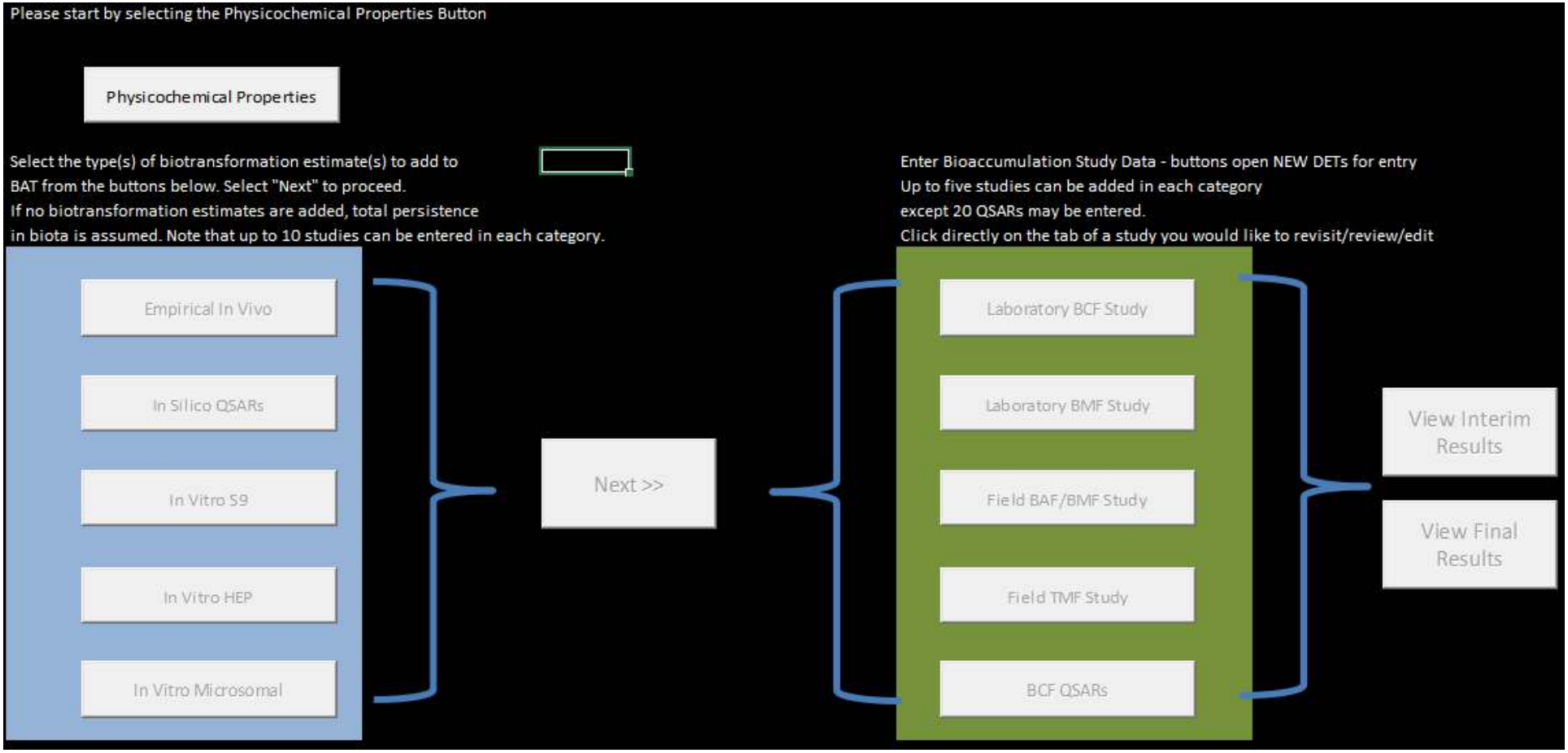
BAT General Workflow



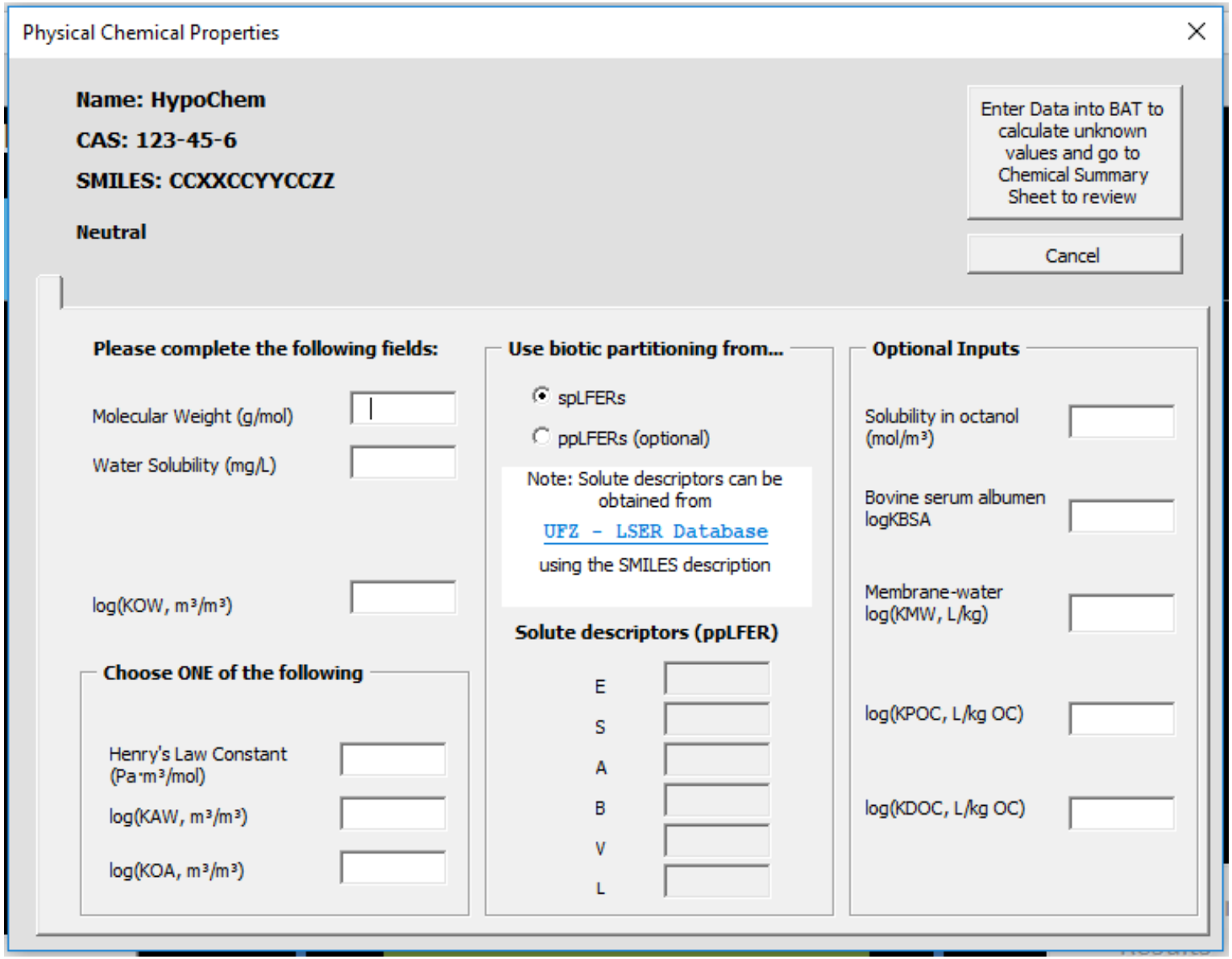
Initialization & Relevance



“BAT Main” Page



Physical-chemical Properties



Biotransformation Rates, e.g. in vitro

IN VITRO BIOTRANSFORMATION TEST - S9

DET	1		Author(s):
Name	HypoChem		Year:
CAS	123-45-6		Title:
SMILES	CCXXCCYYCCZZ		Source:
Key Test Details and Quantitative Information	**FISH**	○ Fish ○ Rodent	
Fish body weight	*	g	
Liver S9 protein content	163	mg/g liver	
Protein concentration	*	mg/mL	
# of timepoints			
Timepoints		h	
# of replicates			
Test chemical initial (nominal) concentration		uM	
Reaction temperature	*	°C	
Reaction pH			
Co-solvent % volume			
Extraction efficiency correction		default = 1	
Slope (always negative for depletion studies)	+	log10[Conc] vs. time (h)	
k_e (first order elimination rate constant)	+	1/h;[=-2.3*slope]	
$CL_{InVitro,INT}$		mL/h/mg protein; [=k/protein conc.]	
$T_{1/2}$ (if reported)		h; [ln(2)/k_e]	
Fraction unbound in test system, $f_{U,S9}$		Enter *	

Once test details are entered:

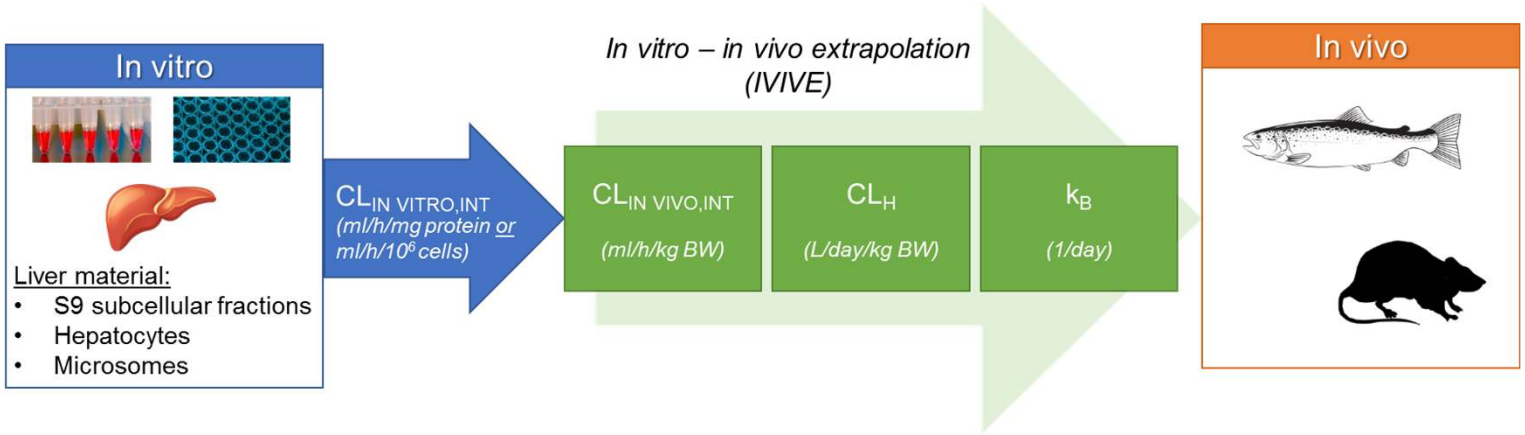
1. Assess Study Reliability HERE
2. Then Calculate IVIVE
3. I'm DONE with this study

Assessment:

Reliability Score:

Input Cell Color Coding:

- Mandatory User Input * Enter one or both of +
- Optional User Input
- Optional User Input/BAT



Data Evaluation Templates (DETs)

Data Evaluation Template (DET)

Quality criteria for evaluating data reliability of a fish o

1	2	3	4	
Is a defined endpoint clearly presented?	Is the (Q)SAR expressed in the form of a transparent and unambiguous algorithm?	Is the (Q)SAR associated with appropriate measures of goodness-of–fit, robustness and predictivity?	Is the (Q)SAR associated with a defined domain of applicability?	Doe prov mec inte the
(Enter Y or N)	(Enter Y or N)	(Enter Y or N)	(Enter Y or N)	(En
Y	Y	Y	Y	

Quality Criteria for Data Reliability of an S9 in vitro biotransformation assay

1. Were the rates and units from the assay clearly presented?	Yes / No
2. Were the source and description of biological material (at least species and mass) provided?	Yes / No
3. Was DMSO used as a co-solvent used for dissolution of test chemical? If so, at what volume fraction?	No / Yes <1%VF / Yes >1%VF
4. Was a (non-DMSO) vehicle (co-solvent) used for dissolution of test chemical? If so, at what volume fraction?	Not Used / VF <0.5% / VF 0.5-1% / VF 1-<2% / VF >2%
5. Were the assay conditions consistent with in vivo (pH, Temp, Co-factors added)?	Reported, Satis. / Assumed, Satis. / Assumed, Not Satis. / NR
6. Was the initial test concentration (Co) reported?	Reported / Assumed, High Conf. / Assumed, Low Conf. / Unknown
7. Was initial concentration (Co) < Michaelis-Menten constant (kMM)? OR first order kinetics confirmed?	Yes / Lit.kMM / Assumed other / Unknown / No
8. LOQ considerations: Measured concentrations ≥ LOQ (or C0 > 10LOQ) OR Measured concentrations < LOQ or not reported	≥LOQ (or C0>10LOQ) / < LOQ / NR
9. Was the protein concentration reported?	Reported / Assumed, High Conf. / Assumed, Low Conf. / Unknown
10. Was the biological material characterized, e.g., activity of EROD, UGT, etc.?	Reported, Satis. / Assumed, Satis. / Assumed, Not Satis. / NR
11. Was the assay duration appropriate?	<= 2h / > 2h / assumed appropriate, > 2h / NR
12. Were there a sufficient number of independent experiments / runs?	Independent Expr: >=3 <3 Unknown; Replicates: >=3 <3
13. Was a negative control used and what were the (loss) results?	<=20% / >20% / NR
14. Was a positive control or a reference chemical used?	Yes, all runs / Yes, some runs / No/NR
15. What was the rate determination method? Substrate depletion (SD) (confirmed or assumed) or product formation (PF) (confirmed or assumed)	SD, confirmed / SD, assumed / PR, confirmed / PR, assumed / NR/ unknown
16. What was the statistical quality of reported rate data?	R2>0.85 or sig. slope, #timepoints>5 / R2<0.85 or NR, #timepoints <6 / unknown
17. What was the chemical purity?	>=98% / >=95% / <95% / NR
18. CRITICAL FAIL (Overall Reliability Score = 0), brief justification required:	☐

Assess Study Reliability

Predicting *HL* from Chemical Structure:

Quantitative Structure-Activity Relationships (QSARs)

Science of the Total Environment 470–471 (2014) 1040–1046

Food and Chemical Toxicology xxx (2017) 1–9

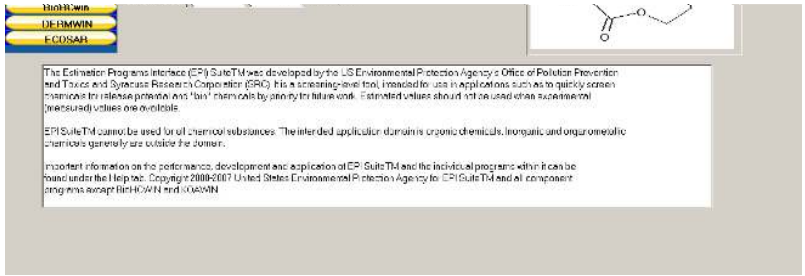
Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Development of human biotransformation QSARs and application for PBT assessment refinement

Ester Papa [a, *], Alessandro Sangion [a], Jon A. Arnot [b, c, d], Paola Gramatica [a]



OECD QSAR Principles 2007

Summary Results

Chemical Identity

Chemical Name: HypoChem
CAS#: 123-45-6
SMILES: CCXXCCYYCCZZ
Neutral (0), Ionic (1): Neutral

View Graphical Results | Return to BAT-Main | Sample Report PDF

													Strength of Evidence:	nB 0.78	B 0	vB 0.22
LOE	Type	Study #	Eco	Org	Kinetic or Steady State	Lipid-corr	Grow-corr	pH	Quality Assessment, QC entries identified as key study deficits (QC = 0)	Min	Value	Max	fugacity ratio	Outcome	Relevance Weighting (0-5)	Reliability Score (%)
BCF	In Silico	1	Aquatic	Generic Lab	SS	Yes	No	7	BAT Estimate	6.59E+02	2.98E+03	1.35E+04	0.04	nB<5000**	3	-
BCF	In Silico	1	Aquatic	Generic Lab Fish	K	Yes	Yes	7	BAT Estimate	6.52E+02	3.06E+03	1.43E+04	0.04	nB<5000**	3	-
BAF	In Silico	1	Aquatic	Generic Low TL Fish	SS	Yes	No	7	BAT Estimate	6.10E+03	2.68E+04	1.18E+05	0.39	vB>5000	4	-
BMF	In Silico	1	Aquatic	Generic Low TL Fish	SS	Yes	No	7	BAT Estimate	0.058	0.253	1.111	0.39	nB<1**	4	-
BMF	In Silico	1	Terrestrial	Wolf	SS	Yes	No	7	BAT Estimate	28.3	28.3	28.3	27.52	vB>1	4	-
BMF	In Silico	1	Aquatic	Generic Lab Fish	SS	Yes	No	7	BAT Estimate	0.081	0.368	1.666	0.32	nB<1**	4	-
BMF	In Silico	1	Aquatic	Generic Lab Fish	K	Yes	Yes	7	BAT Estimate	0.082	0.384	1.799	0.32	nB<1**	4	-
TMF	Field	1	Aquatic	Field	N/A	Yes	N/A	7	18 20 21 22	0.741	0.741	0.741	N/A	nB<1	5	75.64%
BCF	In Silico	1	Aquatic	Total water	N/A	N/A	N/A	7	6	1.68E+03	1.68E+03	1.68E+03	N/A	nB<5000	3	70.59%

The Bioaccumulation Assessment Tool (BAT)
developed by ARC Inc. with support from CEFIC-LRI
Prepared by: Jon
Organization: ARC
Report created on: 2018-09-11 14:19

Bioaccumulation Assessment Report

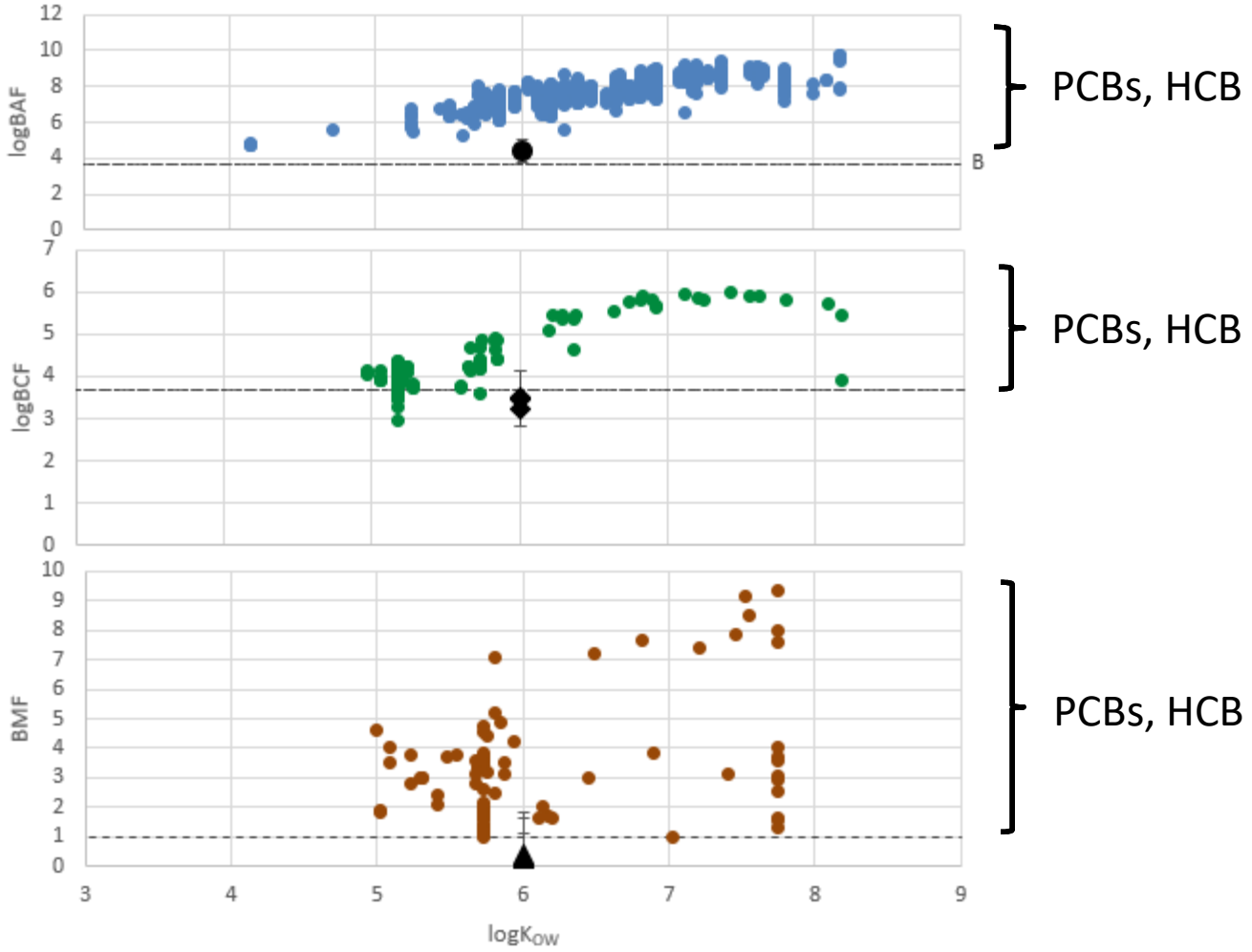
Project Summary

HypoChem **CAS #: 123-45-6**
SMILES: CCXXCCYYCCZZ

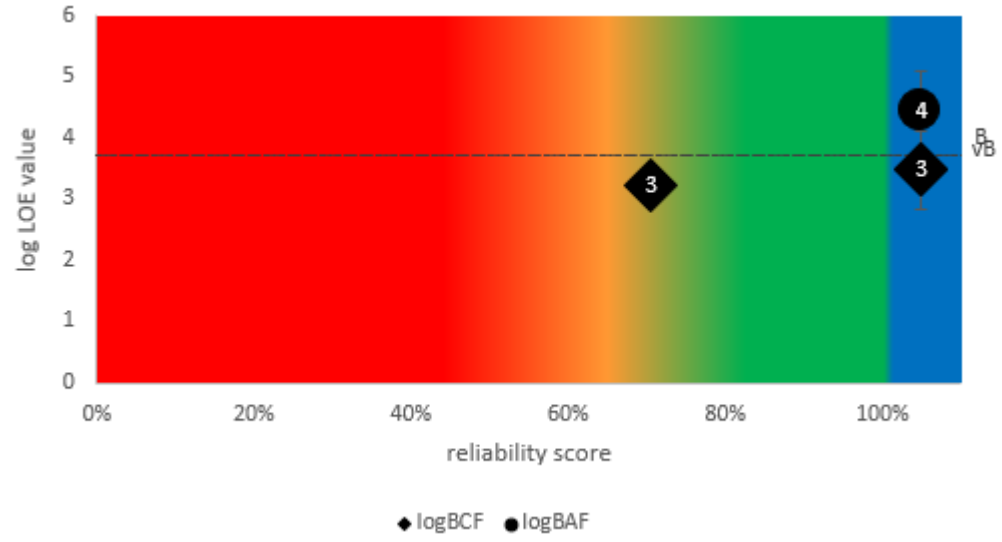
Integrates:

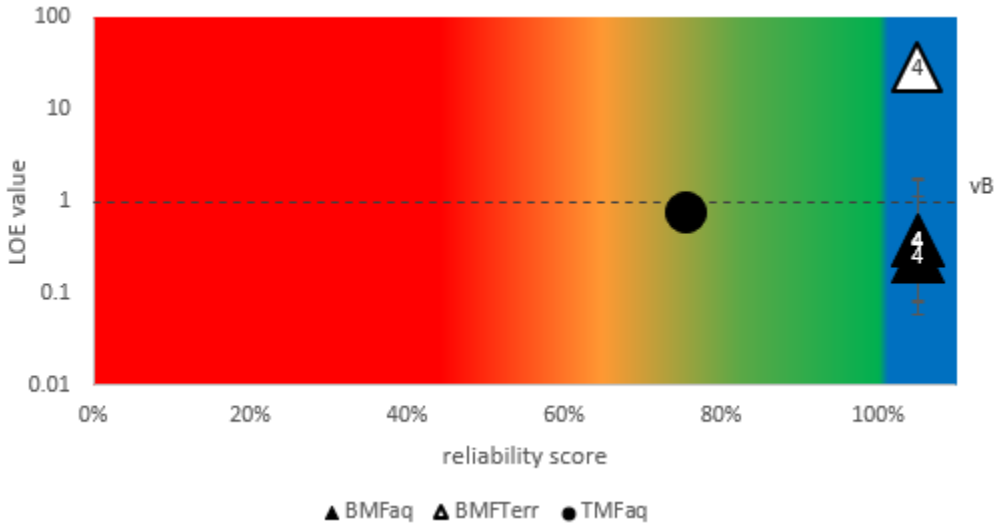
- Various LOEs
- Relevance
- Reliability
- Strength
  - Outcome: nB, B, vB

Summary Plots, e.g. benchmarking

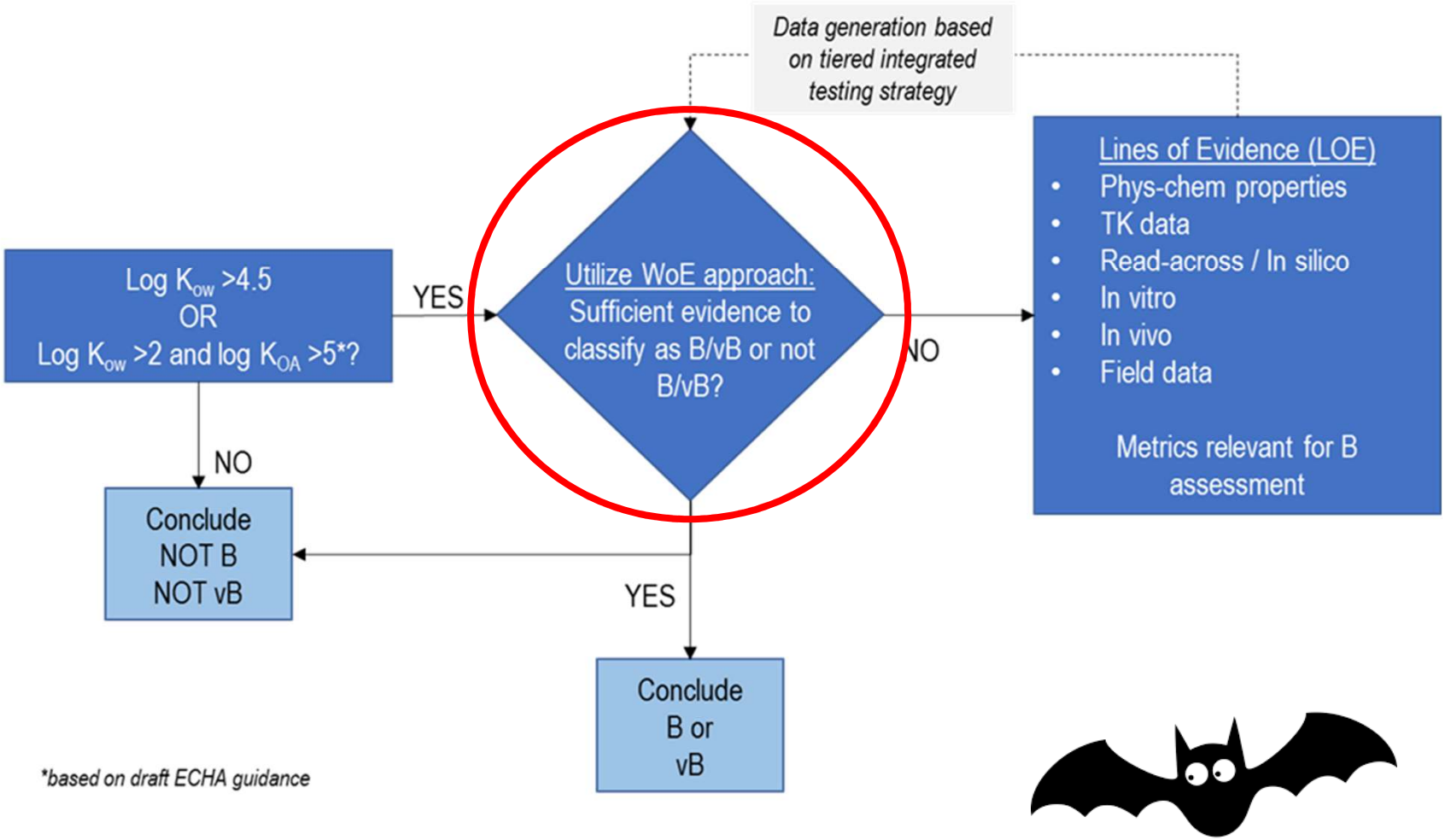


Summary Plots, e.g. LOEs, reliability





Testing Guidance to Address Uncertainty



Summary

- The BAT provides a consistent and transparent QWOE framework for B assessment for aquatic and terrestrial organisms
- Reflects current “state of the science”; can continue to evolve with new standardized methods and approaches
- Can be used for:
  - “data rich” chemicals with multiple empirical LOE
  - “data poor” chemicals with only basic structural information
  - directing new studies to address uncertainty, if necessary
- Serves as an effective communication & educational tool
- Continued feedback after using the BAT is welcome…

Thank you

- The comprehensive user-manual and quick start guide are embedded in the BAT spreadsheet.
- A manuscript outlining the BAT is in preparation.
- The BAT & introductory videos are available on-line at:
  www.arnotresearch.com
  www.cefic-lri.org

- A training course was held in Rome (May 2018) that included the BAT and in vitro and in silico methods for estimating biotransformation rates

- Please contact us if there is interest in additional training courses or workshops:
  jon@arnotresearch.com
  membry@hesiglobal.org

Arnot Research & Consulting

cefic LRI
The Long-range Research initiative