BIOACCUMULATION & EXPOSURE CONSIDERATIONS

NASEM Sunscreen Study

05 August 2021

Michelle Embry, Health & Environmental Sciences Institute (HESI)

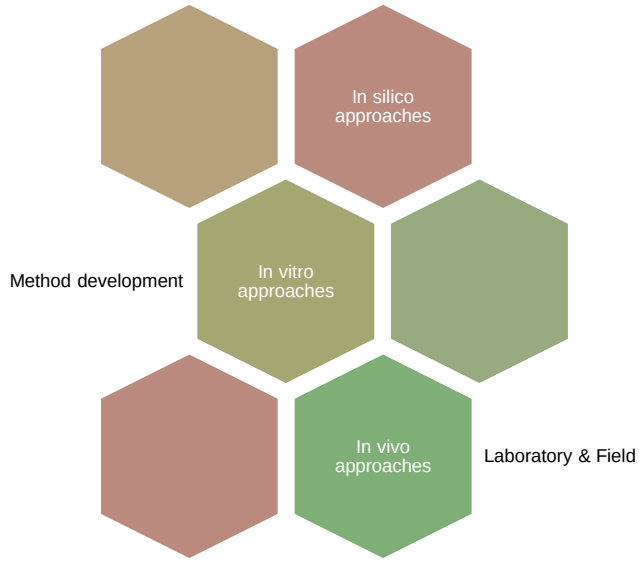
OUTLINE

- Bioaccumulation basics
- Exposure and toxicokinetics
- Octocrylene example
- Take home messages

HESI BIOACCUMULATION COMMITTEE

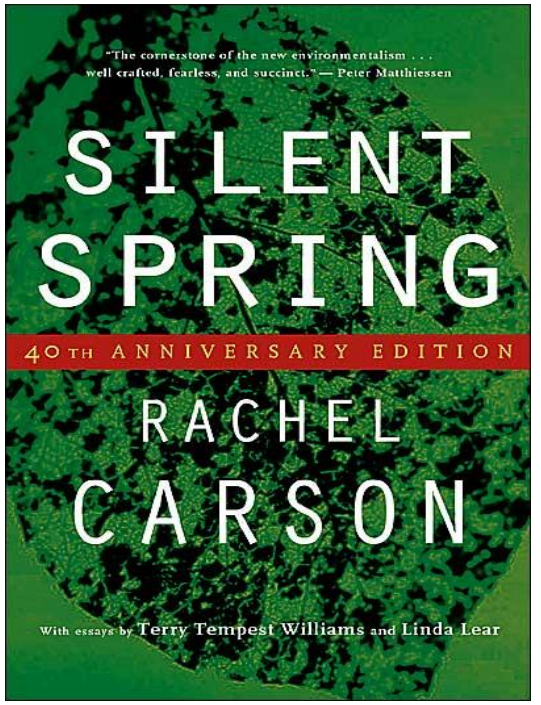
- Started in 2005
- **Mission:** To develop the tools needed for assessing the potential bioaccumulation of organic chemicals and address how metrics used to assess bioaccumulation can be integrated to develop a weight-of-evidence approach for deriving assessment conclusions.

  - 8 large, international workshops
  - >35 publications
  - 2 OECD test guidelines (TG 319 A&B)
  - Numerous international partnerships and collaborative research activities



BIOACCUMULATION: WHY DOES IT MATTER?

- DDT / DDE & raptor population declines; PCBs with worldwide distribution; biomagnification up the food chain
- National and international regulatory programs have traditionally focused on identifying and controlling chemicals that are Persistent, Bioaccumulative, and Toxic (**PBT**) to prevent (or ban) these types of chemicals
- Beyond PBT classification, **bioaccumulation is important for risk assessment more broadly**
- **B quantifies relationships between external and internal exposure!**



“B” DEFINITIONS

- **BIOACCUMULATION**: the process that causes an increased chemical concentration in an organism compared to that in its ambient environment through all exposure routes.
  - **BIOCONCENTRATION:** the net accumulation of a chemical by an organism as a result of uptake directly from its surrounding environment (respiration or dermal) [**not diet!**] – measured in controlled laboratory experiments (i.e., OECD 305)
  - **BIOMAGNIFICATION:** the increase in concentration from prey to predator from dietary exposure – measured in controlled laboratory experiments (i.e., OECD 305) and field.

“B” METRICS

For new chemicals, most common sources of information to evaluate bioaccumulation potential:

1. Octanol-water partition coefficient (Kow)
2. Laboratory bioconcentration factor (BCF) (e.g., OECD TG 305-I & II) [fish] – aqueous exposure
3. Laboratory biomagnification factor (BMF) (e.g., OECD TG 305-III) [fish] – dietary exposure
4. Laboratory bioaccumulation factor (BAF) (e.g., OECD TG 315, 317) [oligochaetes] – environment + diet
5. Laboratory biota sediment accumulation factor (BSAF) (USEPA EPA 600/R-99/064) [oligochaetes, bivalves]

*Field-based methods are available:

6. Field BAF
7. Field BMF
8. Field BSAF
9. Trophic magnification factor (TMF)

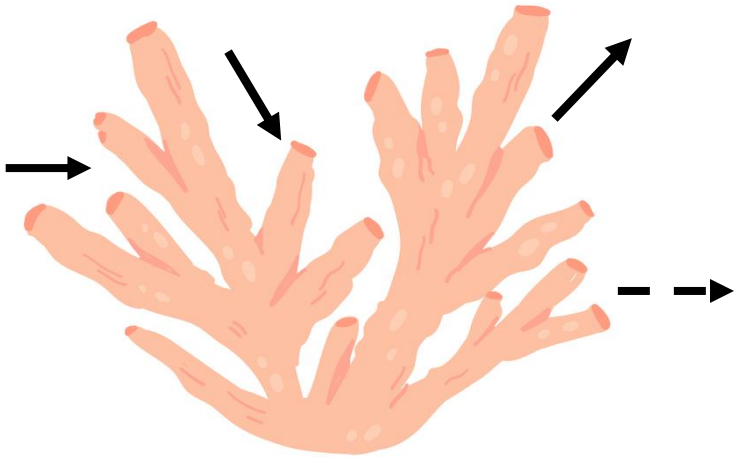
Most evaluations performed in / for fish

BIOACCUMULATION CONCEPTS

- Many mathematical models (QSARs) using K_{OW}-based relationships predict bioaccumulation correctly for many compounds if they are not biotransformed
- Biotransformation tends to reduce bioaccumulation
- Biotransformation is the most critical uncertainty in bioaccumulation assessments
- Available fish k_B QSARs
- New OECD TG (319 A&B) to measure *in vitro*

What does this look like for corals?

$$\text{Coral BCF} = \frac{\text{Concentration in coral}}{\text{Concentration in water}}$$



$$C_{coral} = \frac{[(? \; C_W) + (? \; C_D)]}{(? + ?)}$$

$$\frac{\text{Uptake}}{\text{Elimination}}$$

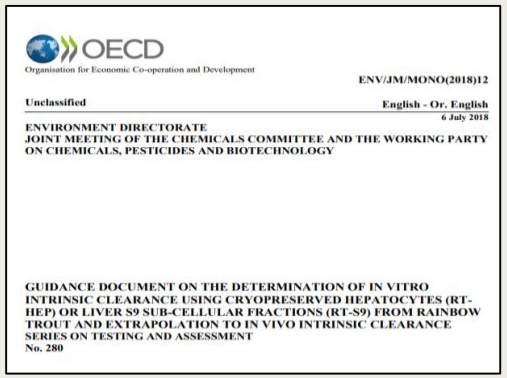
LINKS: BIOTRANFORMATION


SOT Society of Toxicology www.toxsci.oxfordjournals.org ToxSci 20 Years

Reliability of *In Vitro* Methods Used to Measure Intrinsic Clearance of Hydrophobic Organic Chemicals by Rainbow Trout: Results of an International Ring Trial

John Nichols,* Kellie Fay,†,‡ Mary Jo Bernhard,§ Ina Bischof,¶ John Davis,‖ Marlies Halder,‖ Jing Hu,‖ Karla Johanning,‖ Heike Laue,# Diane Nabb,** Christian Schlechtriem,¶ Helmut Segner,†† Joe Swintek,‡ John Weeks,‡ and Michelle Embry‖,1

https://www.ncbi.nlm.nih.gov/pubmed/29767801


OECD

Organisation for Economic Co-operation and Development

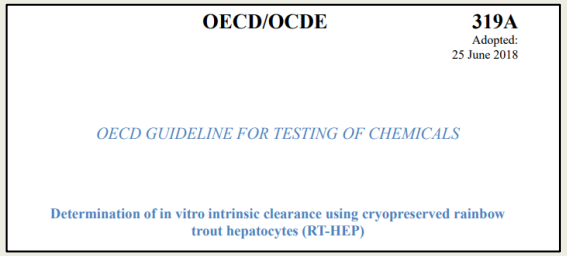
ENV/JM/MONO(2018)12

Unclassified — English - Or. English — 6 July 2018

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

GUIDANCE DOCUMENT ON THE DETERMINATION OF IN VITRO INTRINSIC CLEARANCE USING CRYOPRESERVED HEPATOCYTES (RT-HEP) OR LIVER S9 SUB-CELLULAR FRACTIONS (RT-S9) FROM RAINBOW TROUT AND EXTRAPOLATION TO IN VIVO INTRINSIC CLEARANCE
SERIES ON TESTING AND ASSESSMENT
No. 280

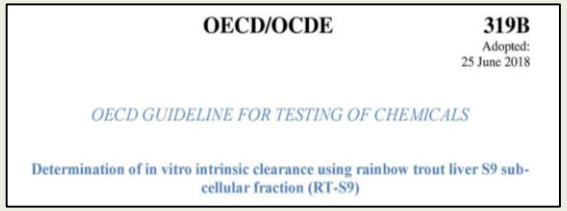
http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2018)12&doclanguage=en


OECD/OCDE 319A Adopted: 25 June 2018

OECD GUIDELINE FOR TESTING OF CHEMICALS

Determination of in vitro intrinsic clearance using cryopreserved rainbow trout hepatocytes (RT-HEP)

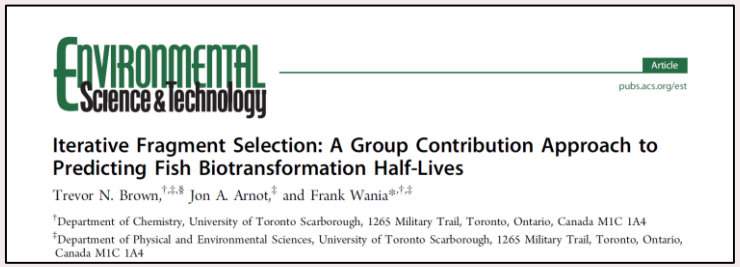
https://www.oecd-ilibrary.org/environment/test-no-319a-determination-of-in-vitro-intrinsic-clearance-using-cryopreserved-rainbow-trout-hepatocytes-rt-hep_9789264303218-en


OECD/OCDE 319B Adopted: 25 June 2018

OECD GUIDELINE FOR TESTING OF CHEMICALS

Determination of in vitro intrinsic clearance using rainbow trout liver S9 sub-cellular fraction (RT-S9)

http://www.oecd.org/publications/test-no-319b-determination-of-in-vitro-intrinsic-clearance-using-rainbow-trout-liver-s9-sub-cellular-fraction-rt-s9-9789264303232-en.htm

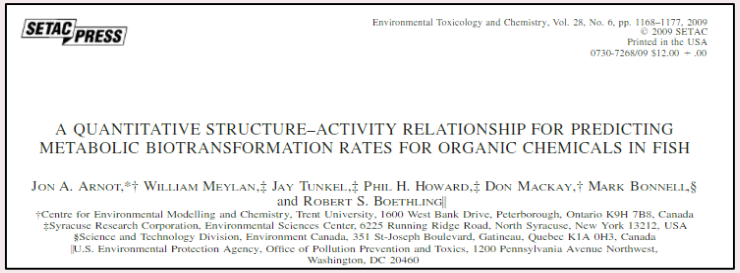

Environmental Science & Technology — Article — pubs.acs.org/est

Iterative Fragment Selection: A Group Contribution Approach to Predicting Fish Biotransformation Half-Lives

Trevor N. Brown,†,‡,§ Jon A. Arnot,‡ and Frank Wania*,†,‡

†Department of Chemistry, University of Toronto Scarborough, 1265 Military Trail, Toronto, Ontario, Canada M1C 1A4
‡Department of Physical and Environmental Sciences, University of Toronto Scarborough, 1265 Military Trail, Toronto, Ontario, Canada M1C 1A4

https://pubs.acs.org/doi/pdf/10.1021/es301182a


SETAC PRESS — Environmental Toxicology and Chemistry, Vol. 28, No. 6, pp. 1168–1177, 2009 © 2009 SETAC Printed in the USA 0730-7268/09 $12.00 + .00

A QUANTITATIVE STRUCTURE–ACTIVITY RELATIONSHIP FOR PREDICTING METABOLIC BIOTRANSFORMATION RATES FOR ORGANIC CHEMICALS IN FISH

Jon A. Arnot,*† William Meylan,‡ Jay Tunkel,‡ Phil H. Howard,‡ Don Mackay,† Mark Bonnell,§ and Robert S. Boethling‖

†Centre for Environmental Modelling and Chemistry, Trent University, 1600 West Bank Drive, Peterborough, Ontario K9H 7B8, Canada
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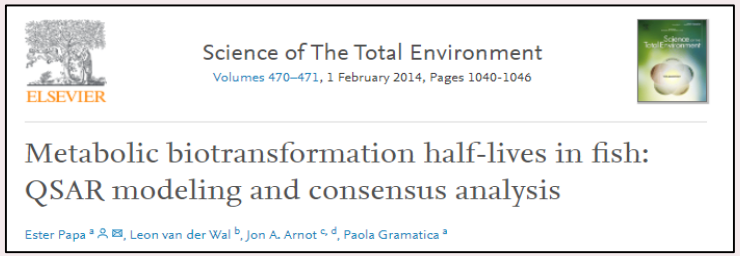
§Science and Technology Division, Environment Canada, 351 St-Joseph Boulevard, Gatineau, Quebec K1A 0H3, Canada
‖U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, 1200 Pennsylvania Avenue Northwest, Washington, DC 20460

https://setac.onlinelibrary.wiley.com/doi/epdf/10.1897/08-289.1


ELSEVIER

Science of The Total Environment
Volumes 470–471, 1 February 2014, Pages 1040-1046

Metabolic biotransformation half-lives in fish: QSAR modeling and consensus analysis

Ester Papa [a], Leon van der Wal [b], Jon A. Arnot [c, d], Paola Gramatica [a]

https://doi.org/10.1016/j.scitotenv.2013.10.068


Journal of COMPUTATIONAL CHEMISTRY

SOFTWARE NOTE | Open Access

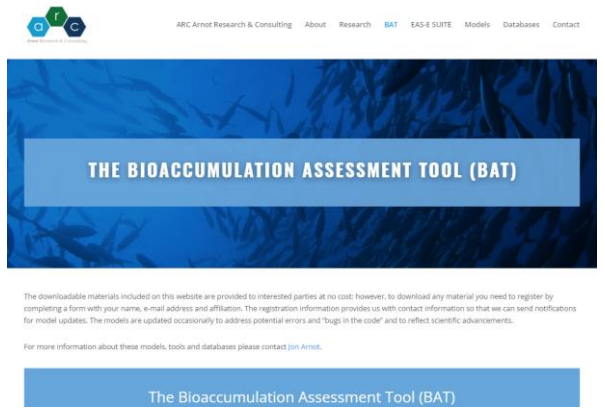
QSARINS-Chem standalone version: A new platform-independent software to profile chemicals for physico-chemical properties, fate, and toxicity

Nicola Chirico, Alessandro Sangion, Paola Gramatica, Linda Bertato, Ilaria Casartelli, Ester Papa

https://doi.org/10.1002/jcc.26551

BIOACCUMULATION ASSESSMENT TOOL (BAT)

- Developed with stakeholder involvement including representatives from academia, government and industry and research support from CEFIC-LRI and ACC-LRI
- Developed to support higher-tier B assessments; integrates measured information & model estimates
- Follows OECD weight of evidence approach
- Guides the collection, generation, evaluation, and integration of various lines of evidence to aid bioaccumulation assessment



www.arnotresearch.com

WHAT CAN THIS INFORMATION TELL US?

- Test methods developed using representative organisms
- For ecological assessment, the protection goal is the ecosystem; need to consider the implications to the broader food web (e.g., not just what is happening in a fish!)

SETAC PRESS

Environmental Toxicology and Chemistry, Vol. 23, No. 10, pp. 2343–2355, 2004

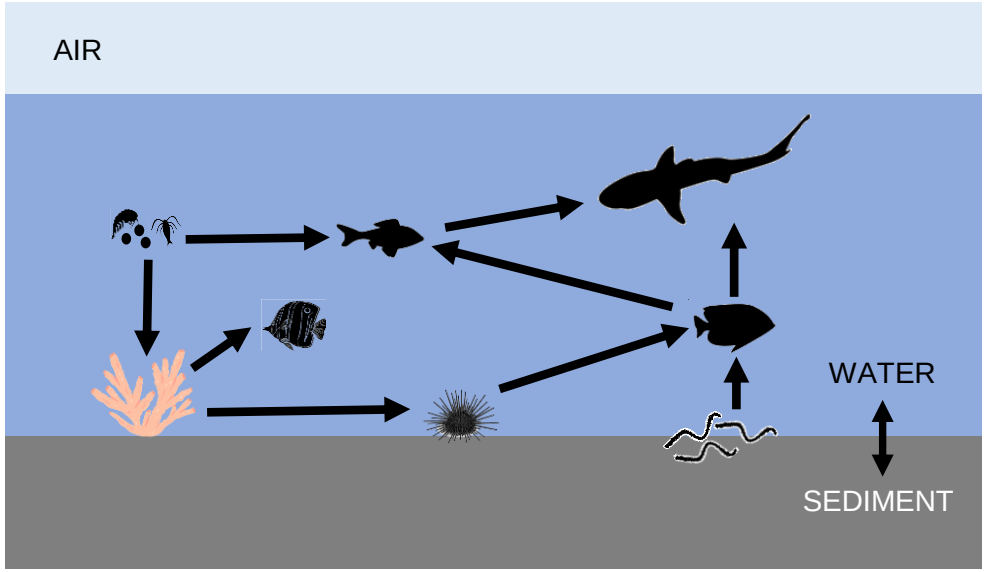
Printed in the USA
0730-7268/04 $12.00 + .00

Special Issue Honoring Don Mackay

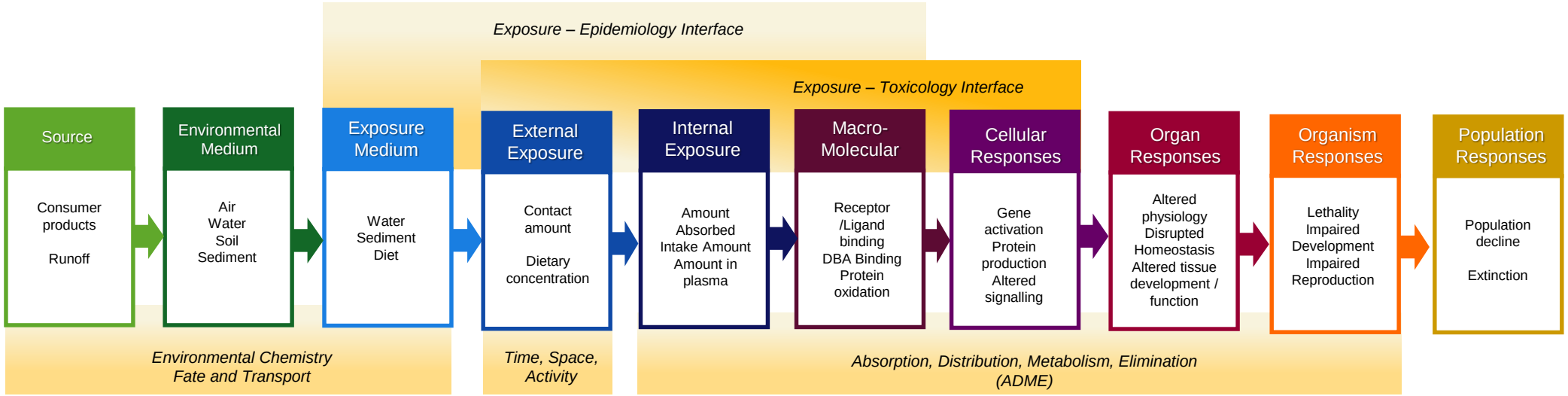
A FOOD WEB BIOACCUMULATION MODEL FOR ORGANIC CHEMICALS IN AQUATIC ECOSYSTEMS

JON A. ARNOT and FRANK A.P.C. GOBAS*
School of Resource and Environmental Management, Simon Fraser University, 8888 University Drive, Barnaby, BC V5A 1S6, Canada

https://doi.org/10.1897/03-438



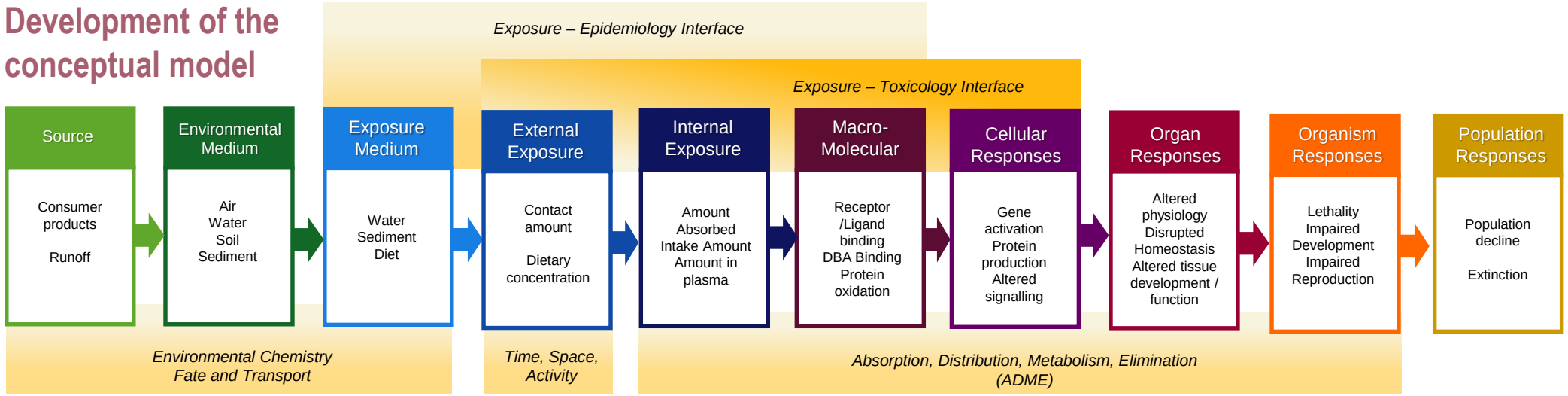
THE BIG PICTURE…



RISK = *ƒ* (hazard x exposure)

"B" information is TK (ADME) information and can inform the exposure-toxicity interface (e.g., beyond criteria)

THE BIG PICTURE…

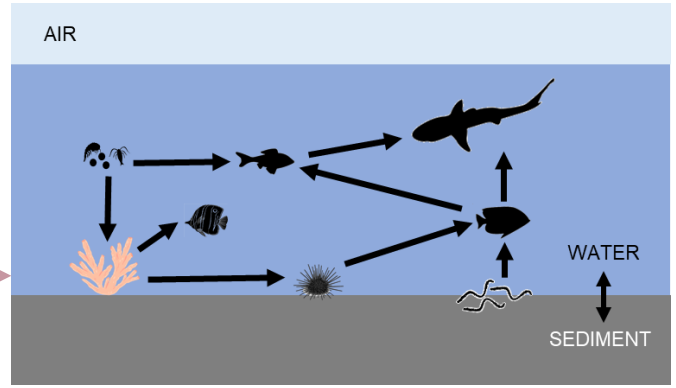


EXPOSURE

- *Chemical "loading rates" to the system*
- *System properties*
- *Chemical persistence (water & sediment half-lives)*
- *Measured & modeled environmental concentrations*

INTERNAL EXPOSURE

- *ADME in relevant species*
- *Holistic ecosystem / food-web approach*



EXAMPLE: OCTOCRYLENE

- Measured log Kow = 6.1; requires additional evaluation for “B” due to log Kow >4.5
- High lipophilicity (log Kow >5) suggests a dietary test is recommended (BMF)
- Biotransformation plays a significant role
  - Saunders et al. 2019: *In vitro* biotransformation in rainbow trout liver S9 (OECD TG 319)
  - QSARS for biotransformation available (in domain)
- Several recent high-quality laboratory in vivo studies available:
  - Saunders et al., 2020: *In vivo* BMF fish study
  - Pawlowski et al., 2019: *In vivo* BCF and BMF fish studies

STUDY	SPECIES	METRIC / VALUE	NOTES
Saunders et al., 2020 (LAB)	Rainbow trout	BMF (low dose): 0.0167 BMF (mod dose): 0.0048 BMF (high dose): 0.0038	BMF < 1 (nB) *Study showed importance of biotransformation, specifically in the GI; positive controls key to evaluate*
Pawlowski et al., 2019 (LAB)	Rainbow trout	BMF: 0.0335	BMF <1 (nB)
Pawlowski et al., 2019 (LAB)	Zebrafish	BCF (low dose): 830 BCF (high dose): 887	BCF < 2000 (nB) *Values shown are lipid and growth corrected*

TAKE HOME MESSAGES

- Problem Formulation: what is the goal?
  - Understanding impacts of UV filters on coral reef ecosystems (and specific impacts on coral)
  - Progress more towards holistic ecosystem health
- How do we get there?
  - Knowledge of basic physiology & TK of corals and other species within the reef ecosystem
  - How does an external concentration (e.g., water, sediment) relate to internal dose that may cause an effect?
  - How might exposure impact the food web, rather than a specific species / taxa?
  - Can we utilize a critical body residue (CBR) approach to better-understand TK as well as TD in these systems?
    - Tsui et al., 2017 paper – calculation of an $EC(LC)50_{internal}$ for coral [https://doi.org/10.1021/acs.est.6b05211]
- For UV filters, determining “B” criteria (nB, B, vB) using fish is likely not value-added
  - B data are TK data and could be more broadly applied to refine risk assessments if suitable
  - Develop a bioaccumulation test for corals?
- PBT assessment is NOT exposure assessment and NOT risk assessment
- Detection or quantification in tissues ≠ bioaccumulation, but provides key data for exposure & risk estimation

QUESTIONS?

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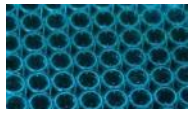
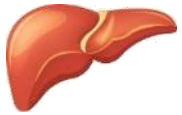
BACKUP

IN VITRO METABOLISM

In vitro

Rainbow Trout Liver:

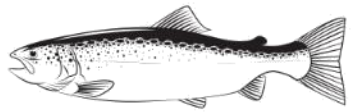
- S9 subcellular fractions
- Cryopreserved hepatocytes

$CL_{IN\ VITRO,INT}$ *(ml/h/mg protein or ml/h/10^6 cells)*

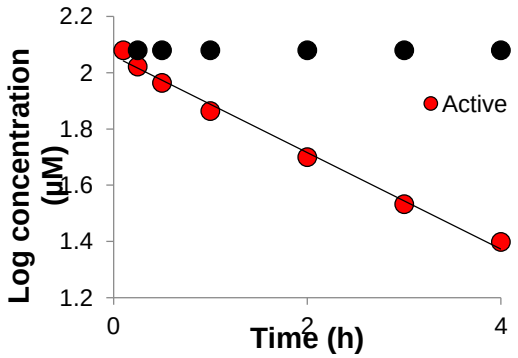
In vitro – in vivo extrapolation (IVIVE)

$CL_{IN\ VIVO,INT}$	CL_H	k_B
(ml/h/kg BW)	*(L/day/kg liver)*	*(1/day)*

In vivo



Combine k_B with estimates of k_1, k_2 and k_E to simulate C_{Fish} and predict BCF (L/kg)



OECD Test Guidelines!
OECD TG 319A&B