Water-Sediment Biodegradation: Challenges in Modeling and Screening for Pharmaceutical Transformation Products

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ABSTRACT

- Given the length of the test period, the analytical expertise and costs associated with conducting the OECD 308 it is often desired that a more rapid screen for assessing the potential transformation of pharmaceuticals would be available. Such information would be helpful in developing the ERA testing strategy especially when the identification of a key transformation product would be helpful early on in the risk assessment; as well as optimizing sampling intervals and conditions for the OECD 308.
- This presentation looks at the observed transformation products identified in the OECD 308 study and compares those to what may be predicted in an expert system to understand how selective the predictions may be and what additional information might be helpful in making a predicted pathway more realistic. Challenges in screening for water-sediment transformations in a laboratory test are also discussed to assess how such a test might be performed. For both situations, case studies will be presented to highlight some of the challenges present in advancing these further.

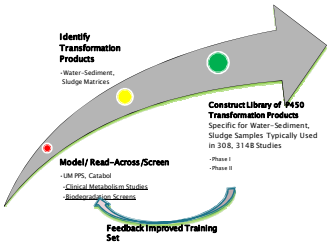
INTRODUCTION

- The potential risk of transformation products (TPs) from wastewater treatment and subsequent water-sediment release environment is a current topic of interest given the advances in analytical chemistry and increase detection of pharmaceuticals and their metabolites in the environment.
- TPs are presumed to be as toxic or less toxic than parent based on known P450 ,MOA, ADH and other mechanisms of transformation and their role in detoxification.
- TPs are generally not considered in the risk assessment (total residue approach) unless there is a need to mitigate a high risk quotient based on the parent compound.

RESEARCH OBJECTIVES

- **Investigate Environmental TPs**
  - Investigate types of transformation products observed in laboratory studies (sludge, water, sediment) conducted in support of the ERA required in product registration
    - Information on about 10 APIs
  - Compare laboratory TP findings to:
    - Human/ non-clinical metabolism: review of literature for structure identification of human/ animal health metabolites
    - University of MN Profile Prediction System (UM-PPS) predictions; or other systems
- **Develop Biodegradation Screens**
  - Develop water-sediment biodegradation screens to facilitate TP identification
- **Establish Library/ Database**
  - Develop TP library based on findings in known matrices to increase specificity of predictions
    - *Identify Opportunities with External Collaborators*

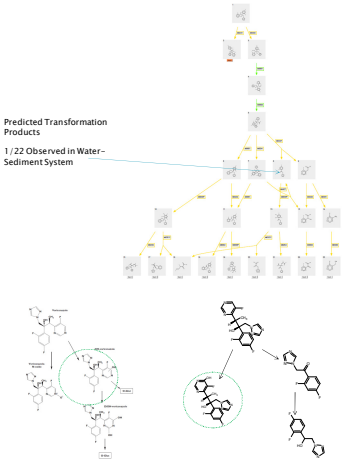
APPROACH



MODEL TRANSFORMATION PRODUCTS

University OF MN Profile Prediction System

VORICONAZOLE

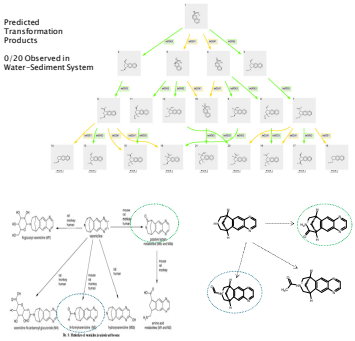


Human Metabolism

Scholz I, et al. 2009. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to CYP2C10 genotype. *JCP* 68 (6) 907- 915

Water-Sediment TPs OECD 308

VARENICLINE



Human Metabolism

Obach S et al. Metabolism and Disposition of Varenicline, a Selective α4β2 Acetylcholine Receptor Partial Agonist, in Vivo and in Vitro. 2006 Drug Metab. and Disp. 34 (1), 121-130

Water-Sediment TPs OECD 308

TP PREDICTIONS

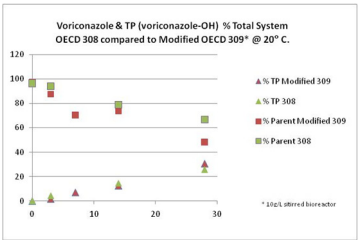
Pharmaceutical	# TPs Observed in OECD 308	Predictions # UM-PPS	Predictions # in Human Metabolism	Predictability of TPs Observed in OECD 308 UM-PPS Sensitivity	UM-PPS Specificity	Human Metabolism Sensitivity	Human Metabolism Specificity
Varenicline	3	20	4	0.00	0.00	0.67	0.50
Voriconazole	3	22	3	0.33	0.05	0.33	0.33

Sensitivity: # TP correctly predicted / total # TP observed
Specificity: # TP correctly predicted/ total # predictions

Human Metabolism- only use environmentally feasible TPs in prediction; no glucuronides, for example.

WATER-SEDIMENT TRANSFORMATION PRODUCT SCREEN

- **Early Development**
  - Convert from sacrificial water-sediment test system to continuous sampling mixed reactor
  - Focus on biomass at water-sediment interface
    - Steps to isolate/ fractionate, clean
    - 2.0 g/L – 10 g/L
    - Modification of OECD 309
  - Options to enhance kinetics
    - Increase temperature; P450 cofactors, other



Acknowledge: Sean McLaughlin- Smithers Viscient Collaboration

ENVIRONMENTAL LIBRARY

CATALOGUE OF AEROBIC BIOTRANSFORMATIONS / MATRIX; N=8 TEST MATERIALS

Reactions		Environmental Source				
	Matrix	Water-Sediment				STP Sludge
	Source	Turkey Creek, MD	Choptank River, MD	Brandywine River, PA	Taunton River & Weweantic Rivers, MA	Groton, CT
Phase I						
-OH		x	x	x	x	
=O				x	x	
-COOH			x	x		
-Sulfate						x
-Dealkylation, Decarbamylation		x	x	x		
Reduction: =O to -OH; Isoxazole		x		x	x	
-Dehydration -C+C- to -C-C-					x	
Phase II						
-N acetyl; -N-formyl		x	x			x

SUMMARY

- Environmental TPs share many common metabolic pathways as with mammalian metabolites
  - Human Health and Animal Health metabolism studies are often available in peer reviewed literature.
- Environmental TP Predictions may not be accurate
  - There may be opportunity to improve predictions based on observed human metabolism
  - While mammalian metabolism provides better basis for predicting TPs observed in water-sediment systems than results from UM-PPS, greater specificity is needed.
- Water-Sediment Biodegradation Screen: on-going research…
  - Success in achieving similar results in mixed reactor design when compared to results from OECD 308 study
  - Need to enhance kinetics to be an effective screen
- Acknowledgements: Andrew Bessire, Tim Ryder and Greg Walker