EPA United States Environmental Protection Agency

EPA Tools and Resources Training Webinar: Chemical Transformation Simulator (CTS)—Predicting PFAS Metabolites and Environmental Transformation Products

Caroline T. Stevens & Eric J. Weber
Center for Environmental Measurement and Modeling
US EPA Office of Research and Development

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Presentation Outline

- Problem: Why was CTS developed?
- Overview of CTS Workflows:
  - Calculate Physicochemical Properties
  - Generate Transformation Products
- CTS Demo
- Development of Reaction Libraries for PFAS Transformations
  - New Jersey Case Study
- Summary and Conclusions

Problem

EPA is required to evaluate the potential for environmental and human health impacts from new and existing chemicals (TSCA & FIFRA).

The Chemical Transformation Simulator (CTS) supports chemical assessments by addressing the following questions:

What chemicals are humans and ecological species exposed to?

- Transformation products can readily form, both in the environment and the body
- Products can be of more concern than the parent chemical

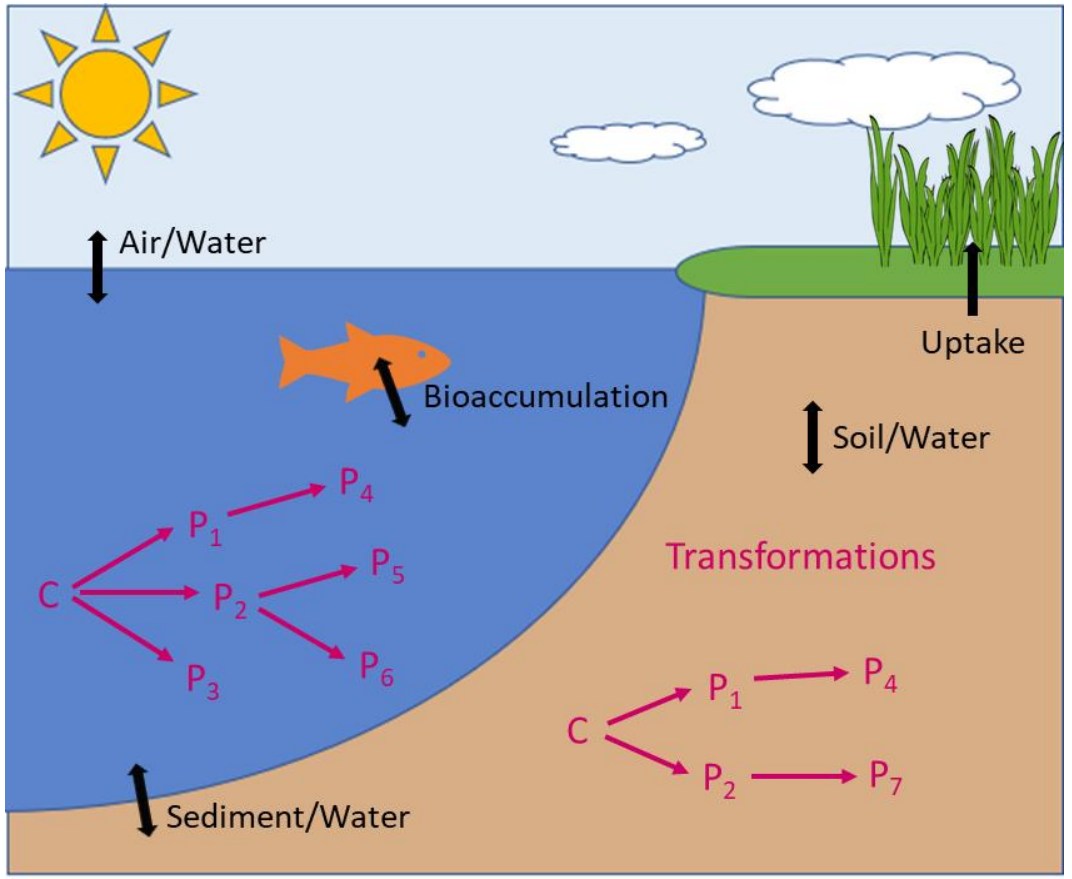
What are the likely routes of exposure to environmental contaminants?

- Physicochemical properties of a chemical control transport and accumulation in environmental compartments (air, water, soil, sediment)

Approach

What does CTS do?

- Identifies **likely transformation products** of organic chemicals in environmental and biological systems
  - Toxicity and properties of products may differ from those of the parent
- Provides estimated and measured **physicochemical property values** for both the parent and products
  - Properties control movement within and between environmental media compartments
  - Properties control partitioning into biological tissues

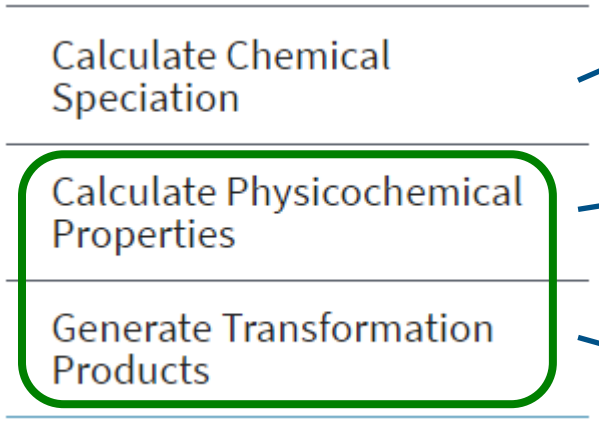


CTS Application

CTS is a web-based tool run on a browser

https://qed.epa.gov/cts/

Three workflows have been developed for user convenience:



Provides ionization constants (pKa values), species distribution as a function of pH, stereoisomer structures, and tautomer distribution at selected pH

Provides calculated physicochemical properties from EPI Suite, T.E.S.T., OPERA, and ChemAxon, as well as available measured values in PHYSPROP

EPI Suite = Estimation Programs Interface Suite
T.E.S.T. = Toxicity Estimation Software Tool
OPERA = OPEn structure–activity/property Relationship App

Provides likely environmental transformation products and metabolites of organic chemicals

CTS Application: Input

- **Step 1:** Identify the chemical of interest by name, CAS ID #, SMILES string, or by drawing the molecular structure
- **Step 2:** Workflow-specific input page

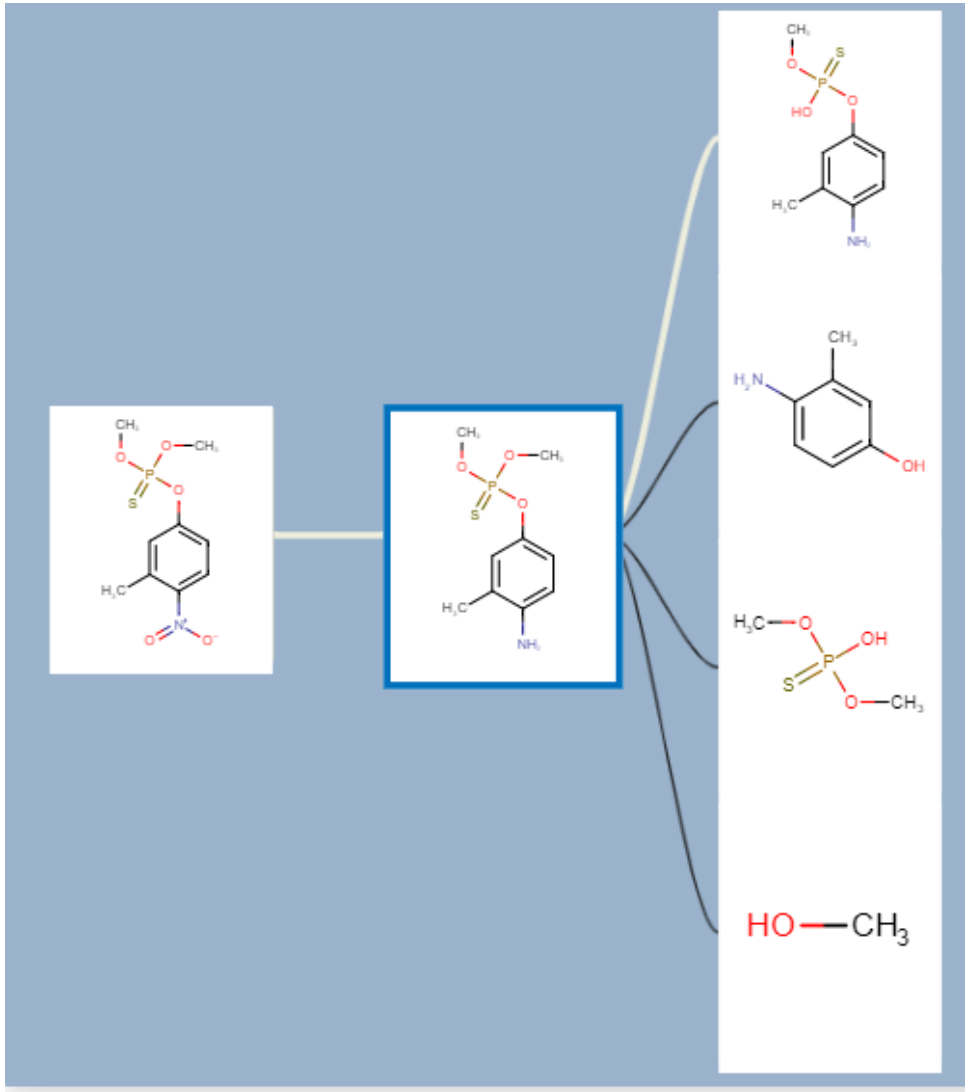
"Calculate Physicochemical Properties" Workflow

- Select properties of interest
- Choose one or more calculators to run

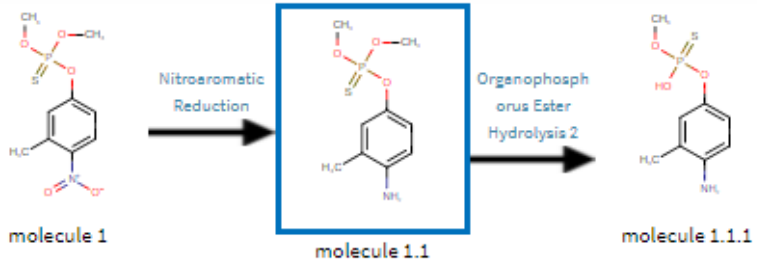
"Generate Transformation Products" Workflow

- Define the scenario of interest (e.g., anaerobic aquatic environments or human metabolism) to select relevant Reaction Libraries

Output from “Generate Transformation Products” Workflow



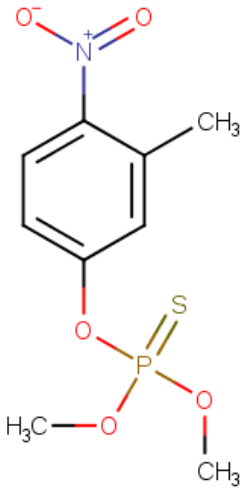
Tree structure diagram showing up to four generations of products

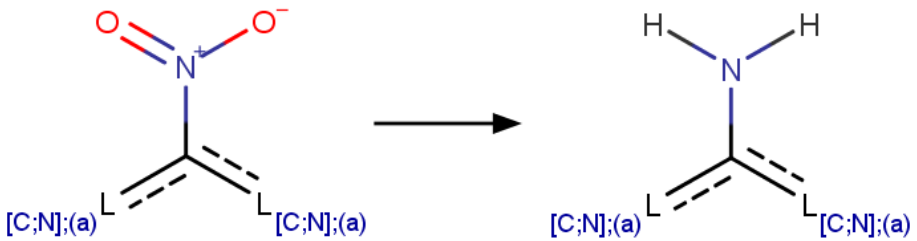


Sequence of transformation reactions

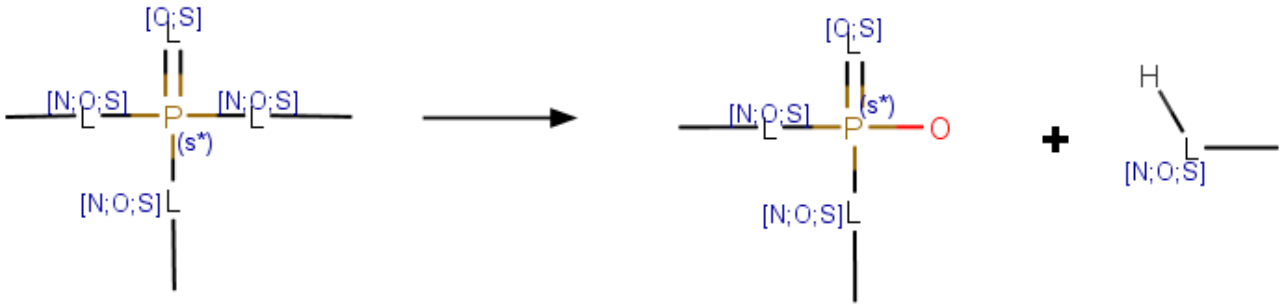
Predicting Transformation Products

Reaction Library: a collection of schemes showing how structural groups on a molecule are modified by a particular transformation process





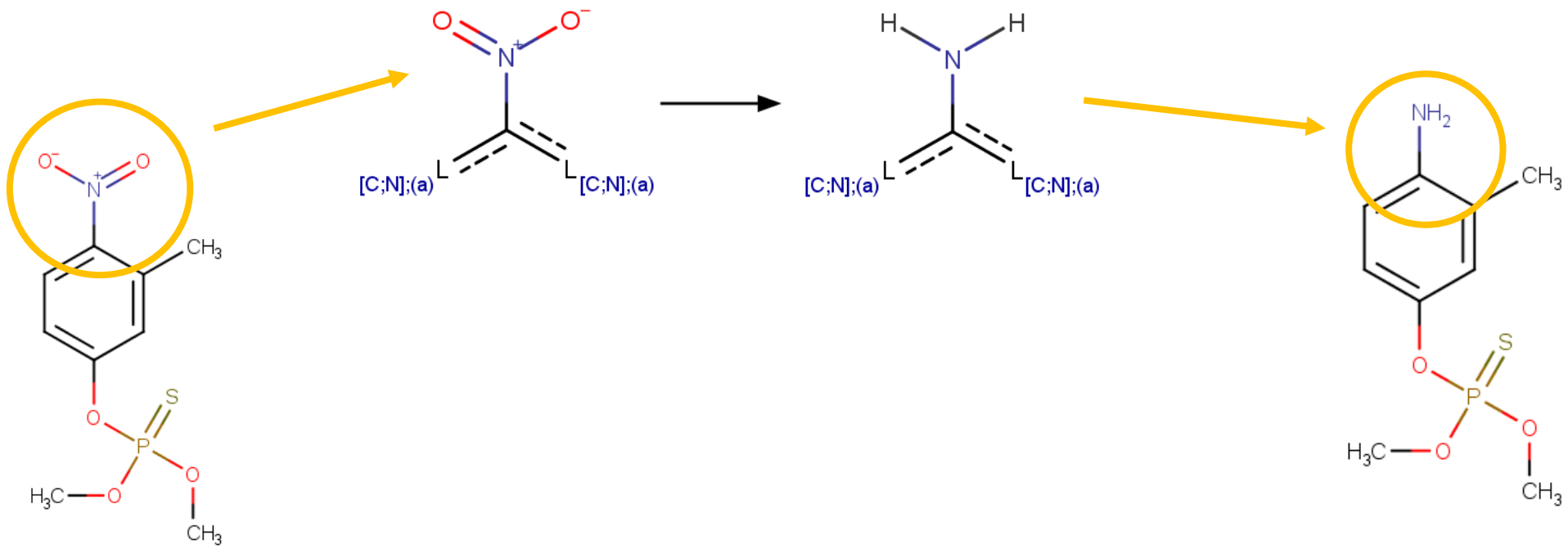
Nitroaromatic reduction scheme



Organophosphorus ester hydrolysis

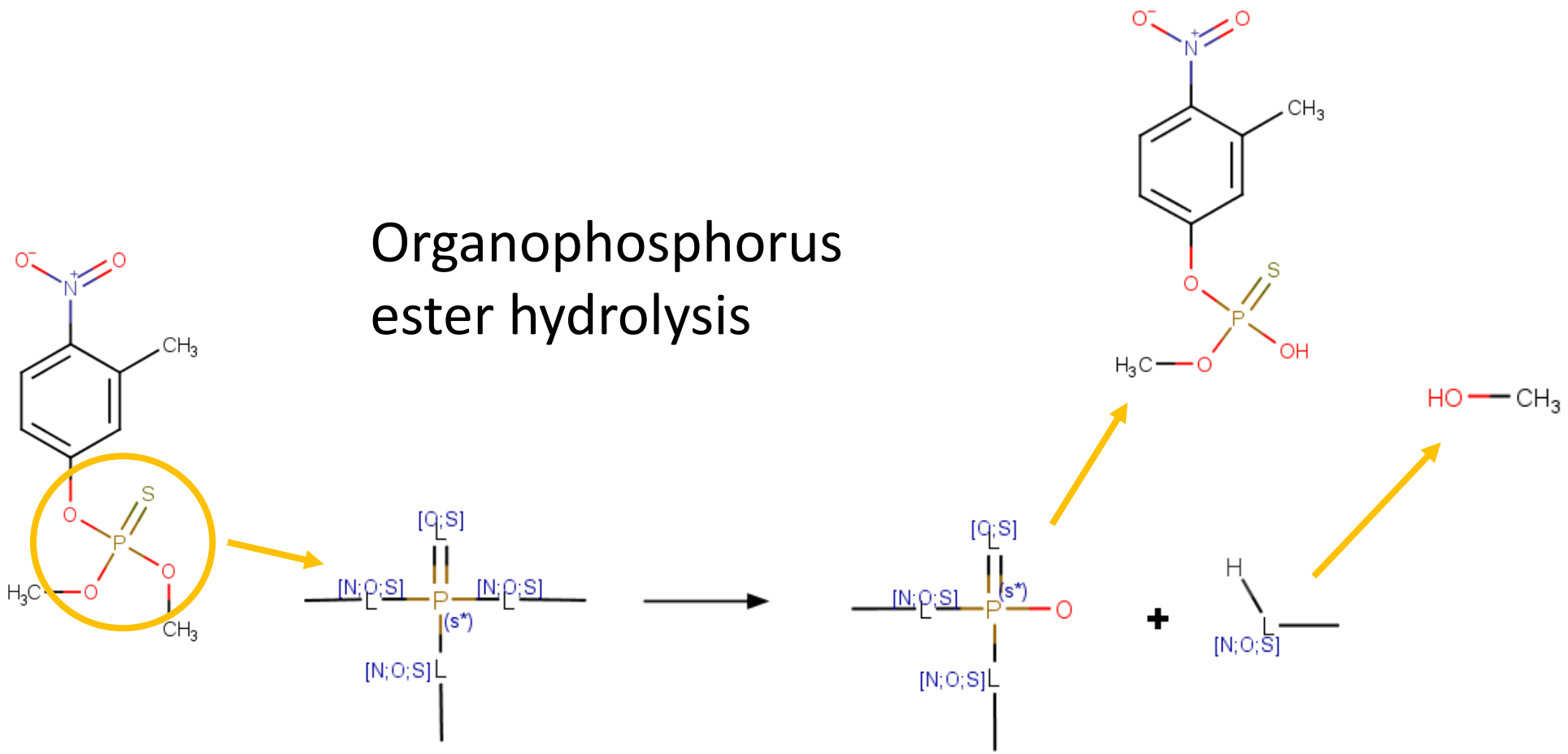
Predicting Transformation Products

Nitroaromatic reduction scheme



Predicting Transformation Products

Organophosphorus ester hydrolysis



Reaction Library Development

- Objectives
  - Correctly predict observed products
  - Minimize false positives (predicted products that are not observed)
  - Identify which of the predicted products are most likely to be observed
- Steps
  - Compile observed transformations (parent/product pairs) and rates from journal articles and regulatory reports
  - Develop reaction schemes from reported transformations
  - Assign scheme ranks based on reported transformation rates
  - Assess performance against test data set
  - Refine schemes and ranks as needed

Assigning Scheme Ranks

Nitroaromatic reduction scheme

Rate data for 34 molecules (n=178)

Median Half-life: 7.7 hours
Range: 1 min to 4.6 days

Rank = 5

Organophosphorus ester hydrolysis

Rate data for 18 molecules (n=39)

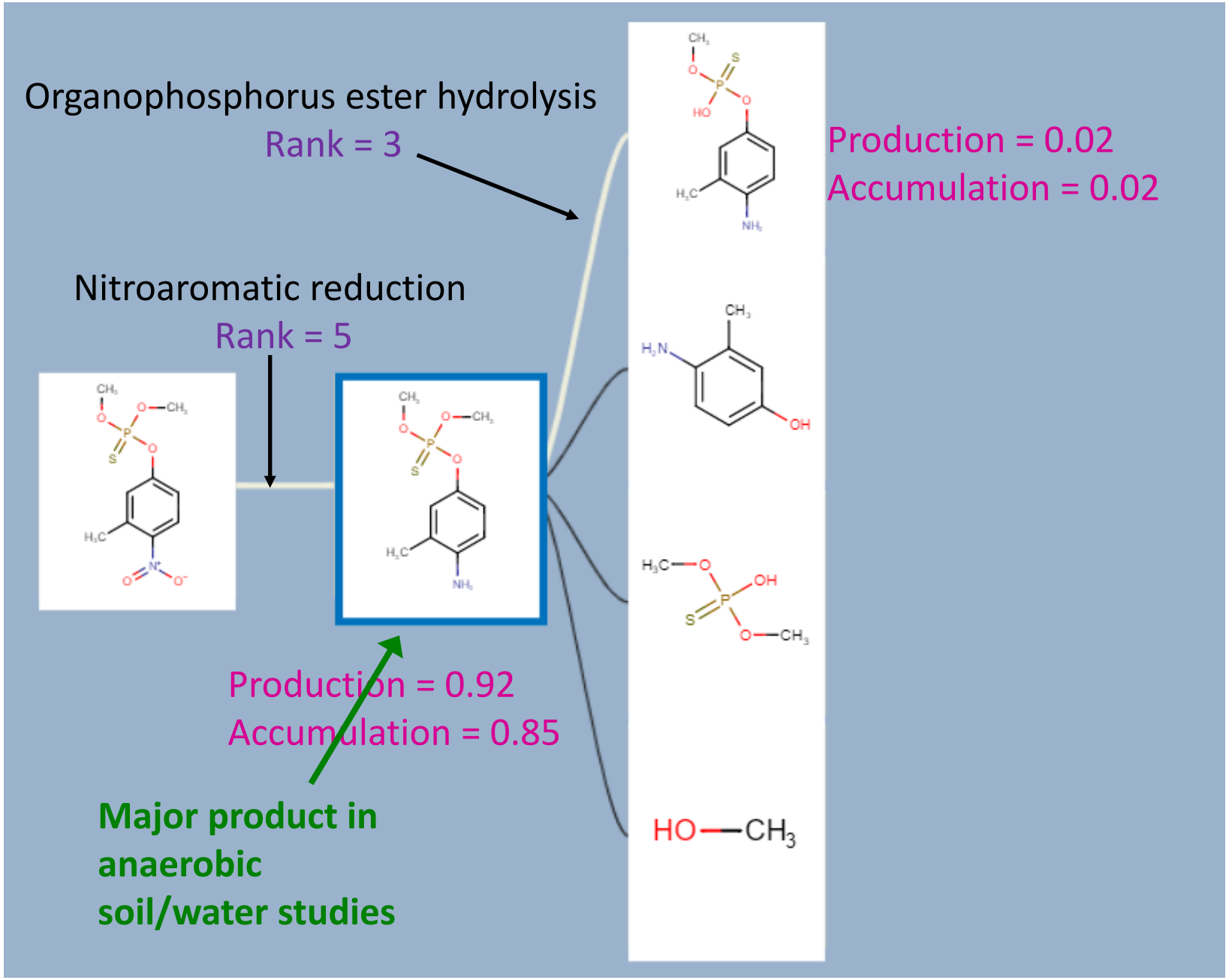
Median Half-life: 44 days
Range: 10 hours to 107 days

Rank = 3

Rank	Half-life Range
7	< 30 min
6	30 min - 200 min
5	200 min - 24 hours
4	24 hours - 7 days
3	7 days - 60 days
2	60 days to 1 year
1	> 1 year

Predicted products of fenitrothion from CTS reaction libraries for abiotic hydrolysis and abiotic reduction

Without ranking, there would be 5 products in the first generation and 6 in the second.



Assessing Reaction Library Performance

Predictions from CTS Reaction Libraries are assessed against observed products reported in the scientific literature or regulatory reports.

Recall (a.k.a. Sensitivity)

- What proportion of the reported transformation products are predicted?

$$Recall = \frac{\#\ of\ correctly\ predicted\ products}{Total\ \#\ of\ reported\ products}$$

Precision (a.k.a. Specificity)

- What proportion of the predicted products have been reported?

$$Precision = \frac{\#\ of\ correctly\ predicted\ products}{Total\ \#\ of\ predicted\ products}$$

Demo of the Chemical Transformation Simulator

Problem: Why the Concern with PFAS?

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are used in many consumer applications due to their stain repellency, ability to form water-proof coatings and use in fire suppression.

The production, application, transport, and disposal of PFAS and PFAS-treated products have resulted in their wide-spread occurrence in environmental and biological systems.

This widespread exposure has prompted toxicity studies, which have linked PFAS to negative health impacts.

Concern over exposure to PFAS and their transformation products has necessitated the development of tools to predict the transformation of PFAS in environmental and biological systems.

Development of a PFAS Reaction Library: Identifying Plausible Transformation Pathways for PFAS

The fact that the PFAS reaction library is based on a specific class of chemicals vs. a specific reaction process (e.g., hydrolysis) presents unique challenges for the construction of the reaction library.

Challenges:

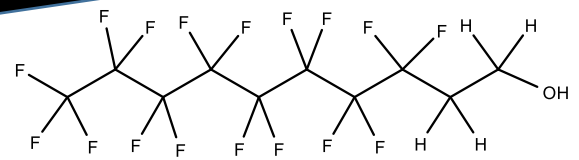
- How do transformation pathways vary across multiple studies from different laboratories for the same reaction system (e.g., aerobic soil)?
- How do transformation pathways vary across relatively different reaction systems (e.g., aerobic soil compared to mixed and isolated bacterial cultures)?
- How do metabolic transformation pathways vary across different species (e.g., fish, humans, and plants)?
- **How does chain length effect transformation pathways and reactivity?**

Environmental:

- Aerobic soil
- Activated sludge
- Anaerobic sediment
- Marine sediment
- Bacterial cultures
- Mixed cultures
- Cultures enriched on substrate
- Pseudomonas sp. Bacteria

Biological:

- Soybean
- Rat
- Rabbit
- Trout
- Carp
- Japanese Medaka
- Earthworm
- Rat, trout and human hepatocytes
- Rat liver cytosol
- Rat and human liver microsomes
- Cytochrome- P450



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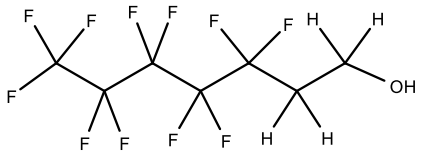


4:2 FTOH

Case Study

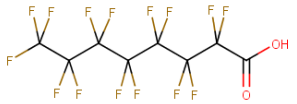
How can the PFAS Reactions Libraries be used to inform ongoing and future studies of PFAS?

(1) Ongoing nontargeted analyses of soils and water for PFAS and their transformation products
(2) Future laboratory studies of the environmental transformation and metabolism of PFAS

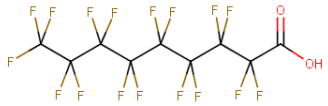
In 2019, the NJ Department of Environmental Protection (DEP) approached EPA

Requested assistance to study PFAS in New Jersey, including whether there was any PFAS associated with two industrial sites, Solvay and Chemours

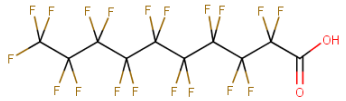
DEP was primarily interested in perfluorocarboxylates:



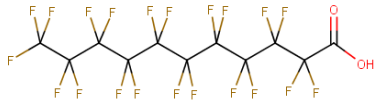
PFOA or C8



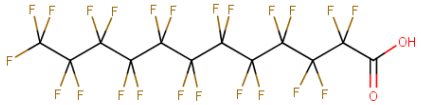
PFNA or C9



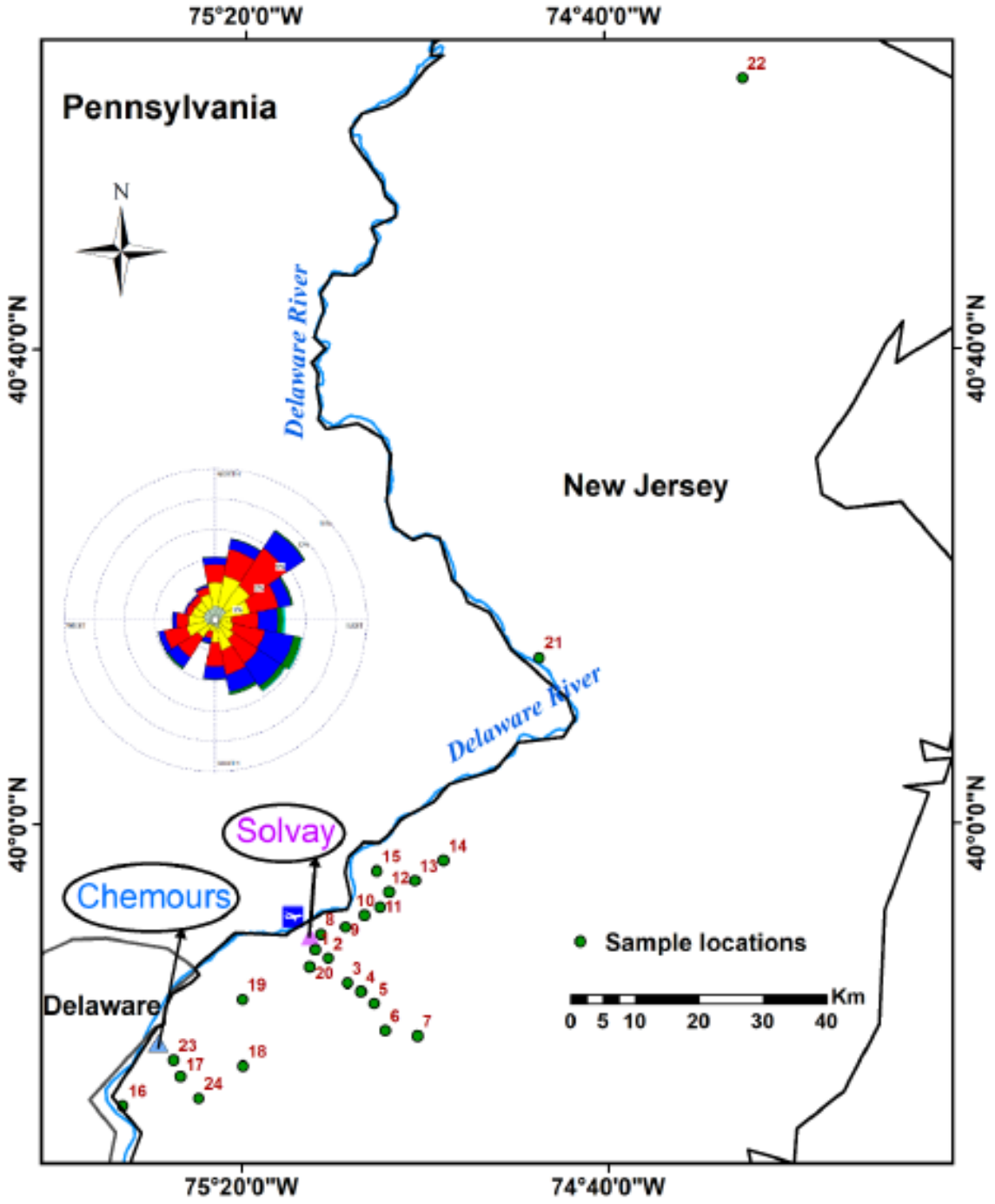
PFDoA or C10



PFUnA or C11



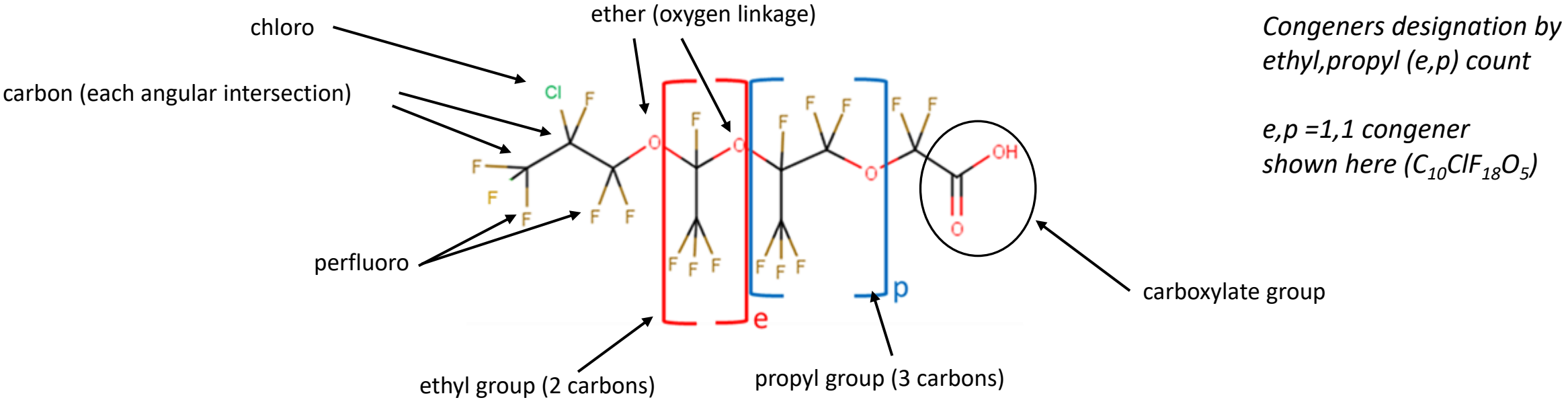
PFDoDA or C12



Nontargeted mass-spectral analyses led to tentative identification of a novel PFAS family

Chloro perfluoro polyether carboxylates (ClPFPECAs or casually “polyethers”)

ClPFPECAs: multiple “congeners” varying in count of ethyl and propyl groups



Congeners designation by ethyl,propyl (e,p) count

e,p =1,1 congener shown here ($C_{10}ClF_{18}O_5$)

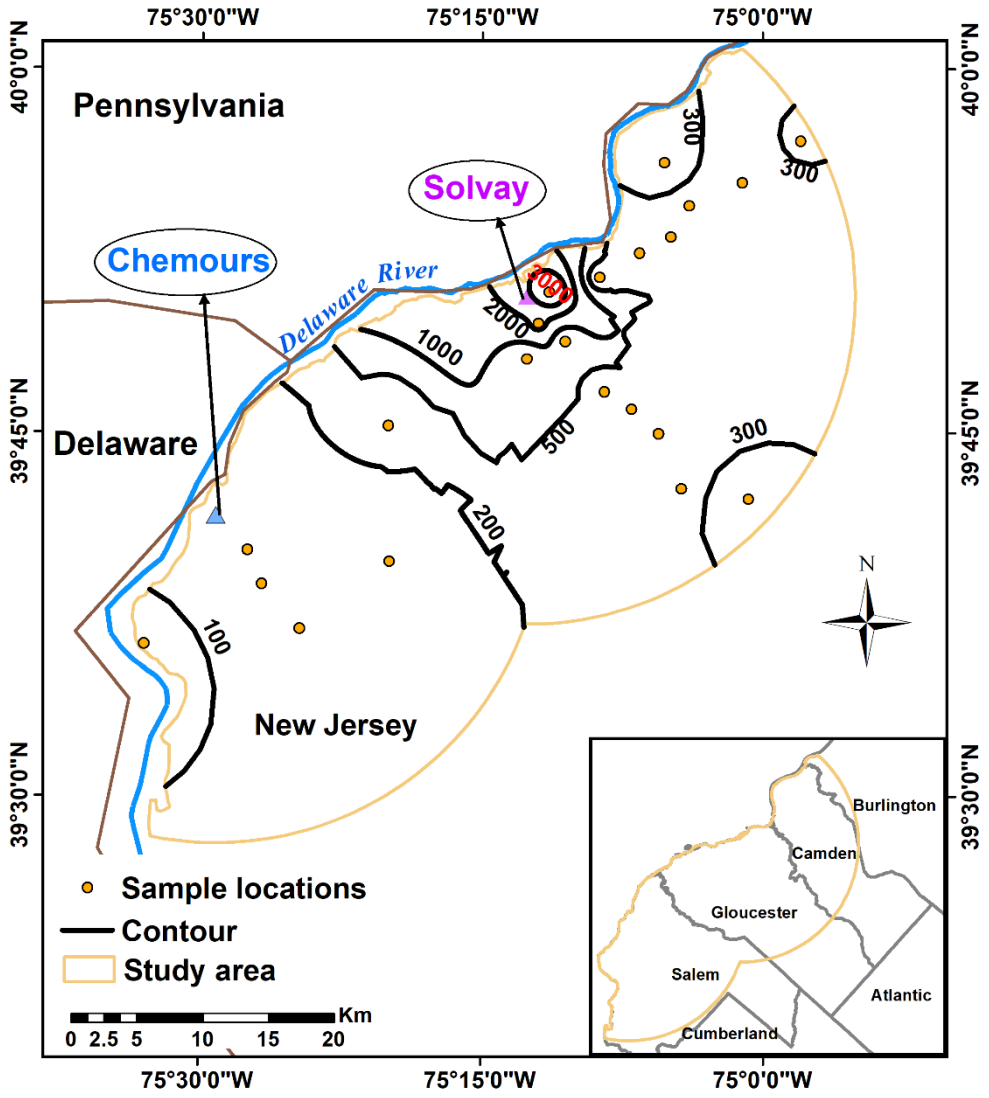
ClPFPECAs appear to be related to Solvay based on literature & data spatial distribution

Data spatial distribution . . .

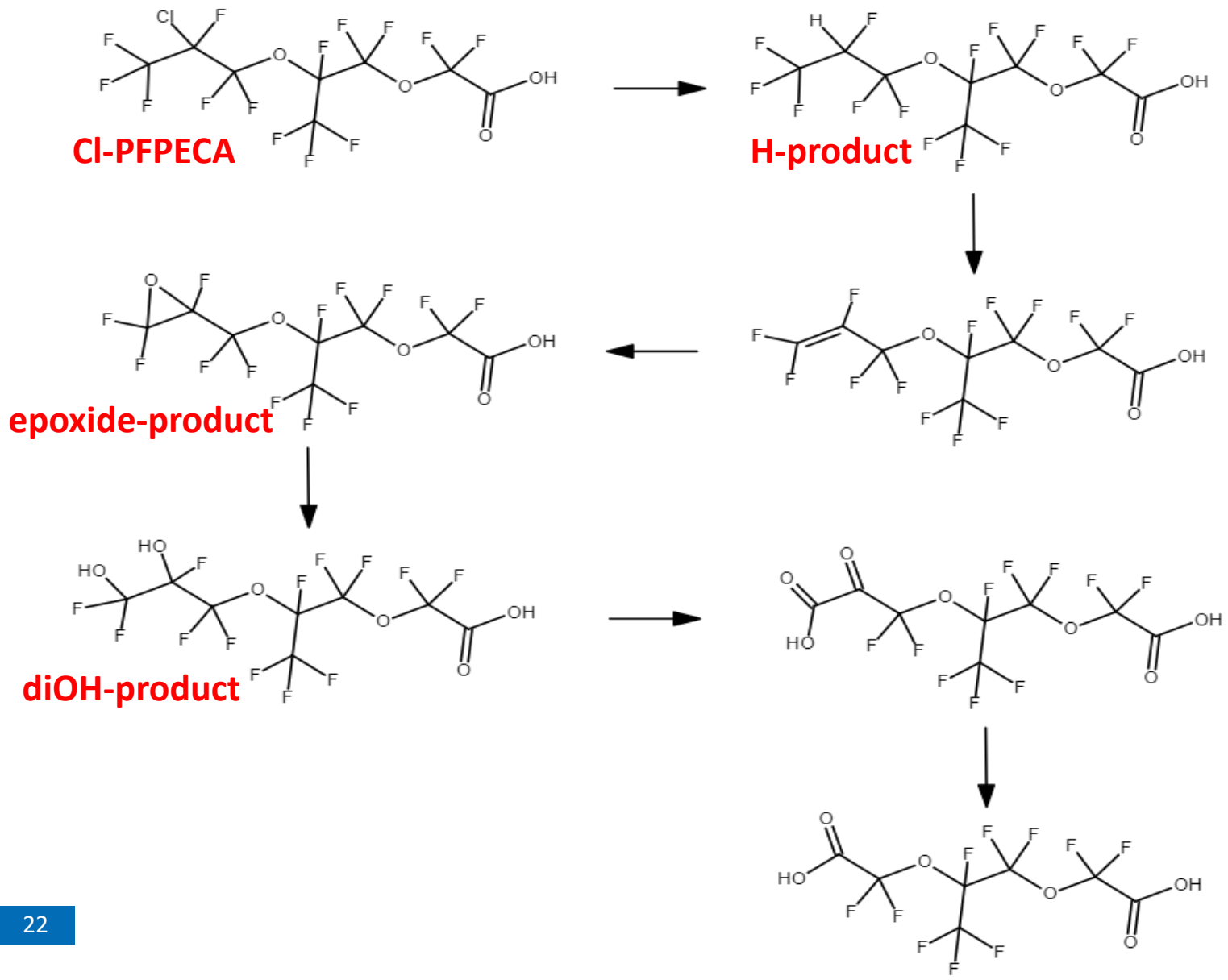
Sum of [ClPFPECA]s contoured with a mathematical algorithm

Yellow arcs are outer limit of modeled area

Bottom line:
Clearly increasing concentration contours with approach to Solvay, more than 10-fold



Transformation Pathway for Cl-PFPECA Predicted by Execution of the PFAS Environmental Reaction Library



Example shown for (0,1) Cl-PFPECA

- These predicted transformation products are expected at low concentrations in nontargeted data
- Three of the predicted transformation products (H-product, epoxide-product and diOH-product) have been identified in NJ soils

Environmental Fate of Cl-PFPECAs: Predicting PFAS Transformation Products in New Jersey Soils

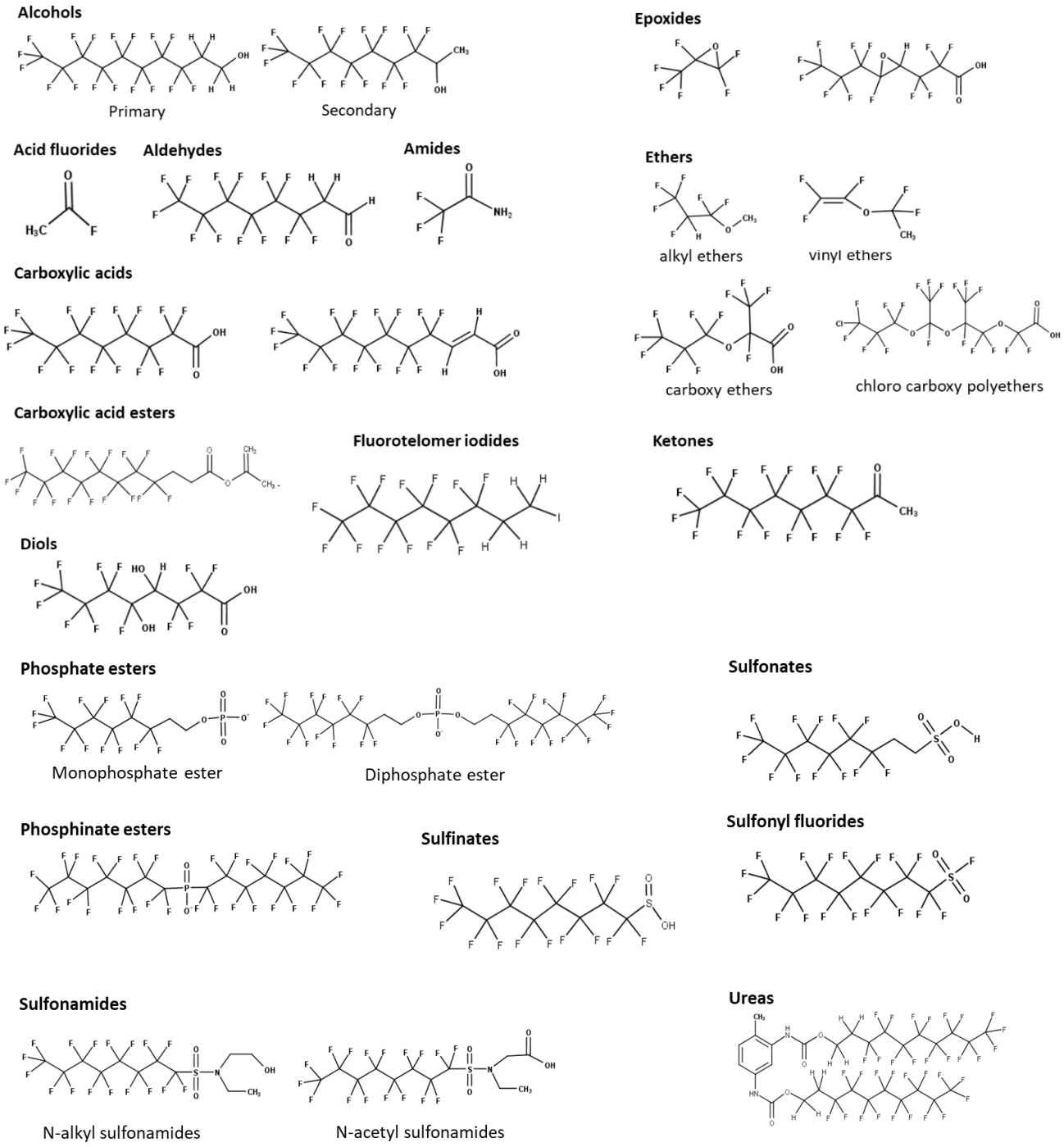
Marina G. Evich, Mary J. B. Davis, Eric J. Weber, Caroline T. Stevens, Brad Acrey, Matthew Henderson, John W. Washington

EPA United States Environmental Protection Agency

Current Results: PFAS Reaction Libraries

The PFAS reaction libraries cover 11 reaction processes (e.g., oxidation and hydrolysis) and 26 PFAS functional groups

Reaction Process	Environmental	Metabolism
Conjugation	0	16
Decarboxylation	2	1
Desulfonation	1	0
Epoxidation	1	1
Hydrolysis	16	11
Hydroxylation	3	1
N-Deacetylation	2	2
N-Dealkylation	1	1
O-Demethylation	0	2
Oxidation	12	8
Reduction	4	5
Total	42	48



Impact

- **Chemical exposure and risk assessors** can use CTS to address data gaps associated with chemical registration and assessment and to support alternative assessment activities for manufactured chemicals.
- **Environmental exposure assessment modelers** can use CTS as a parameterization tool for models that simulate/predict environmental fate, transport, bioaccumulation and dose estimation.
- **Laboratory scientists** can use CTS predictions to help interpret the results of field and laboratory studies.

Take Home Messages

- By expanding chemical assessments to consider the formation of transformation products, CTS helps provide a more holistic evaluation of the potential impacts to humans and ecological species from the manufacture and use of an organic chemical product.
- CTS predicts the likely transformation products of organic chemicals in environmental and biological systems.
- Estimated physicochemical properties are provided for both the parent and the transformation products.

Contact

Caroline Stevens
Environmental Engineer
Center for Environmental Measurement and Modeling
US EPA Office of Research and Development
stevens.caroline@epa.gov
706-540-3936

Eric Weber
Research Chemist
Center for Environmental Measurement and Modeling
US EPA Office of Research and Development
weber.eric@epa.gov
706-355-8224

Try it out: https://qed.epa.gov/cts/

We welcome your feedback and suggestions for improvement!

CTS Development Team

Current Team Members

Caroline Tebes Stevens
Eric Weber
Kurt Wolfe
Rachel Gladstone (ORISE)
Jovian Lazare (ORISE postdoc)
Nick Pope (Contractor)

Former Team Members

Marcy Card (ORISE postdoc)
Jack Jones (retired EPA)
Michaela Koopmans (SSC)
Meredith Martin (SSC)
John Olmstead (SSC)
Jay Patel (ORISE)
Alok Shah (SSC)
Chenyi Yuan (ORISE postdoc)