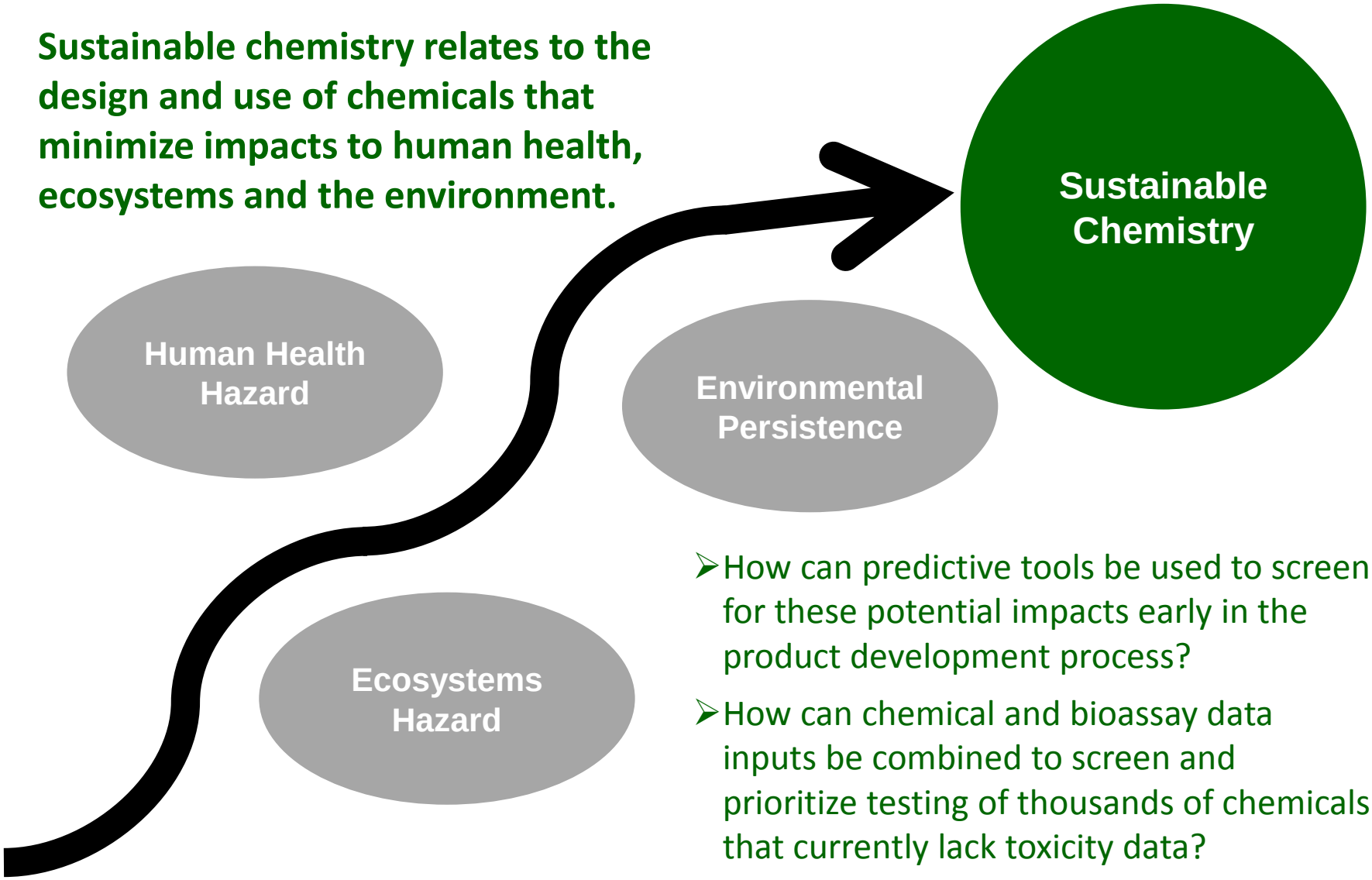
CSS Sustainable Chemistry Research for Exposure Parameter Estimation

Exposure Science in the 21st Century Grantee Kick-off Meeting – *Feb. 3, 2015*

Caroline Stevens
U.S. EPA National Exposure Research Laboratory
Ecosystems Research Division
Athens, GA

Sustainable chemistry relates to the design and use of chemicals that minimize impacts to human health, ecosystems and the environment.

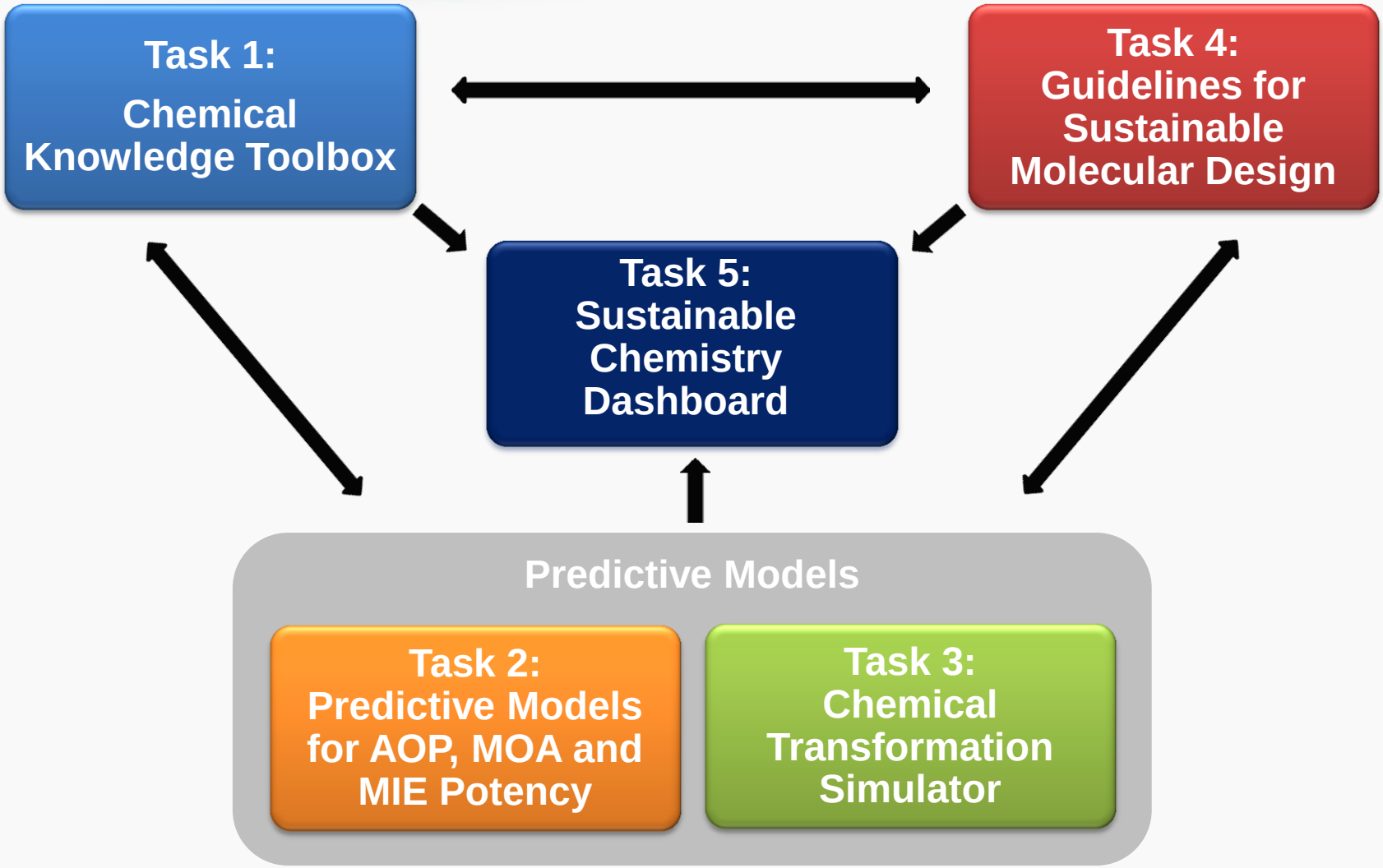


- How can predictive tools be used to screen for these potential impacts early in the product development process?
- How can chemical and bioassay data inputs be combined to screen and prioritize testing of thousands of chemicals that currently lack toxicity data?
- How do chemical transformations impact the hazard potential and environmental persistence?

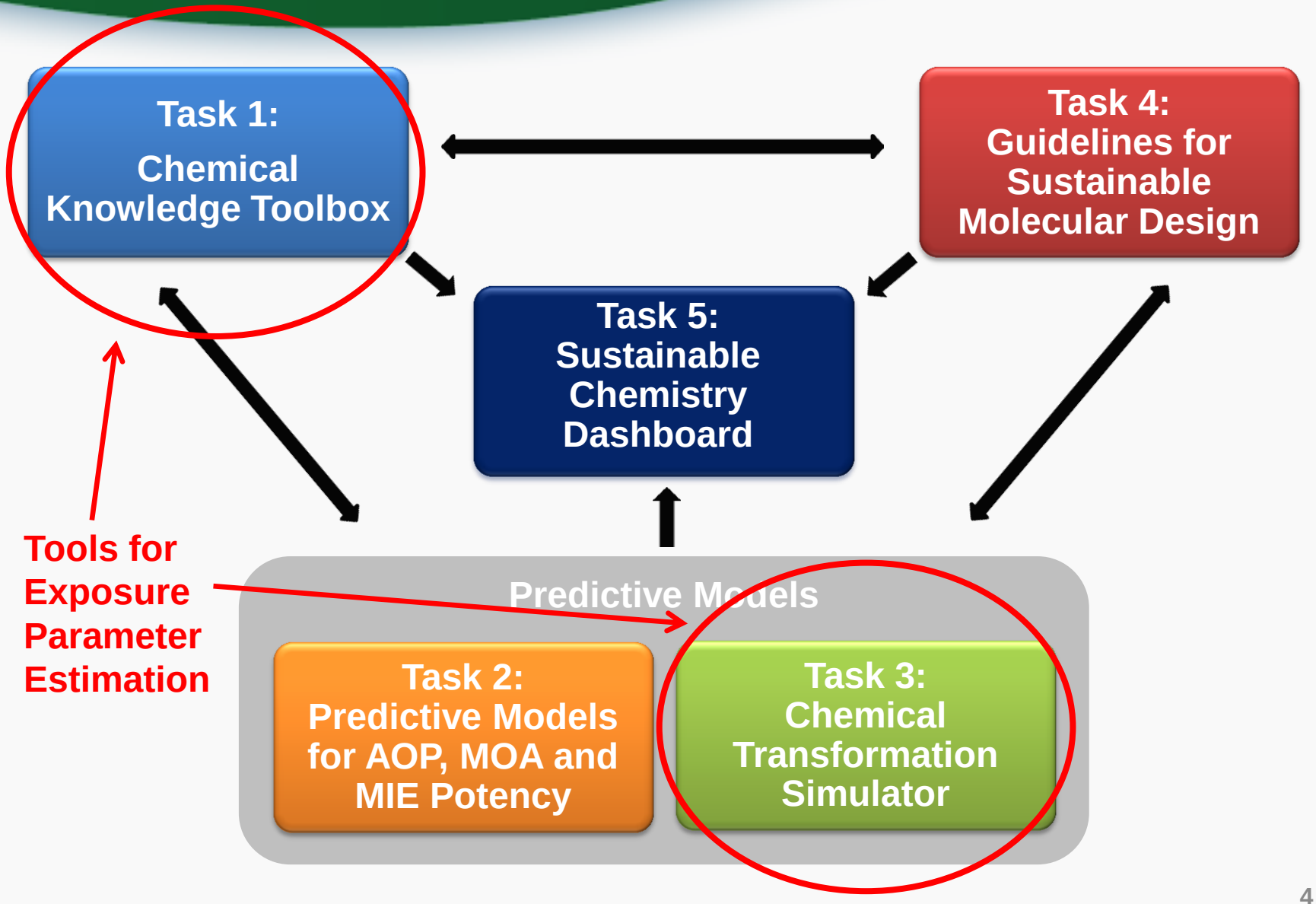
Project Deliverables

- Tools for analyzing and mining chemical space, including structure-based feature sets, chemical clustering schemes, similarity indices, and analog identification methods
- Predictive models for estimating toxicity, persistence, bioaccumulation and transformation potential based on chemical structural features and inherent chemical properties (ICPs)
- Guidance on Sustainable Molecular Design (SMD) of chemical products

Task Organization



Task Organization



Sustainable Chemistry Task 1

Lead: Ann Richard, NCCT

EPA United States Environmental Protection Agency

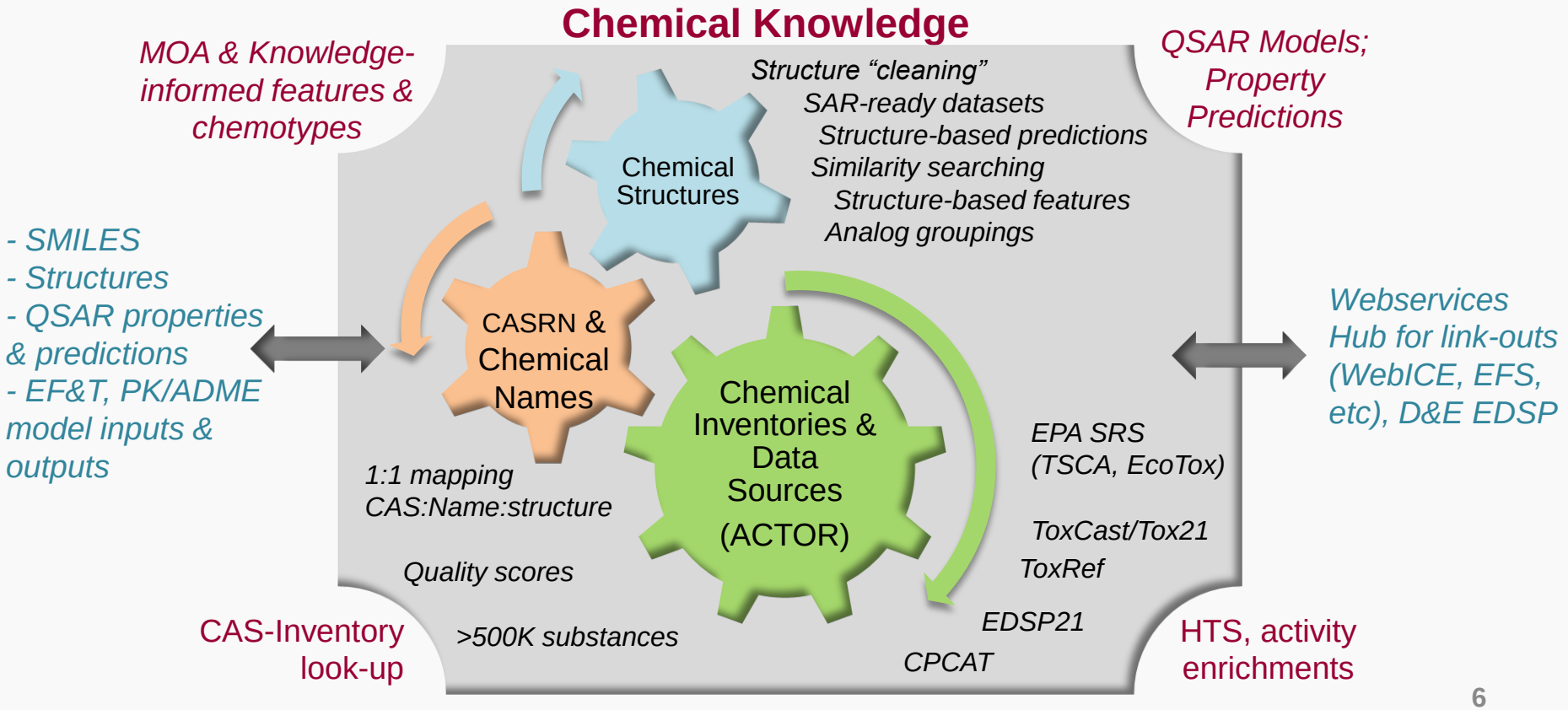
Research Approach

- **Chemical Knowledge Toolbox**
  - Bring together a wide range of previously isolated data (CAS, structures, structure-based properties & predictions)
  - Institute a rigorous, high quality, cheminformatics infrastructure to serve as a hub for CSS and EPA-wide chemical research modeling activities
- **Chemotypes:** knowledge-informed chemical feature sets to support predictive modeling.

Sustainable Chemistry Task 1

Lead: Ann Richard, NCCT

Product 1: Integrated DSSTox(v2)-ACToR Chemical Structure Resource for Linking Chemical Structures/Properties to Use and Hazard Data (**FY15**)



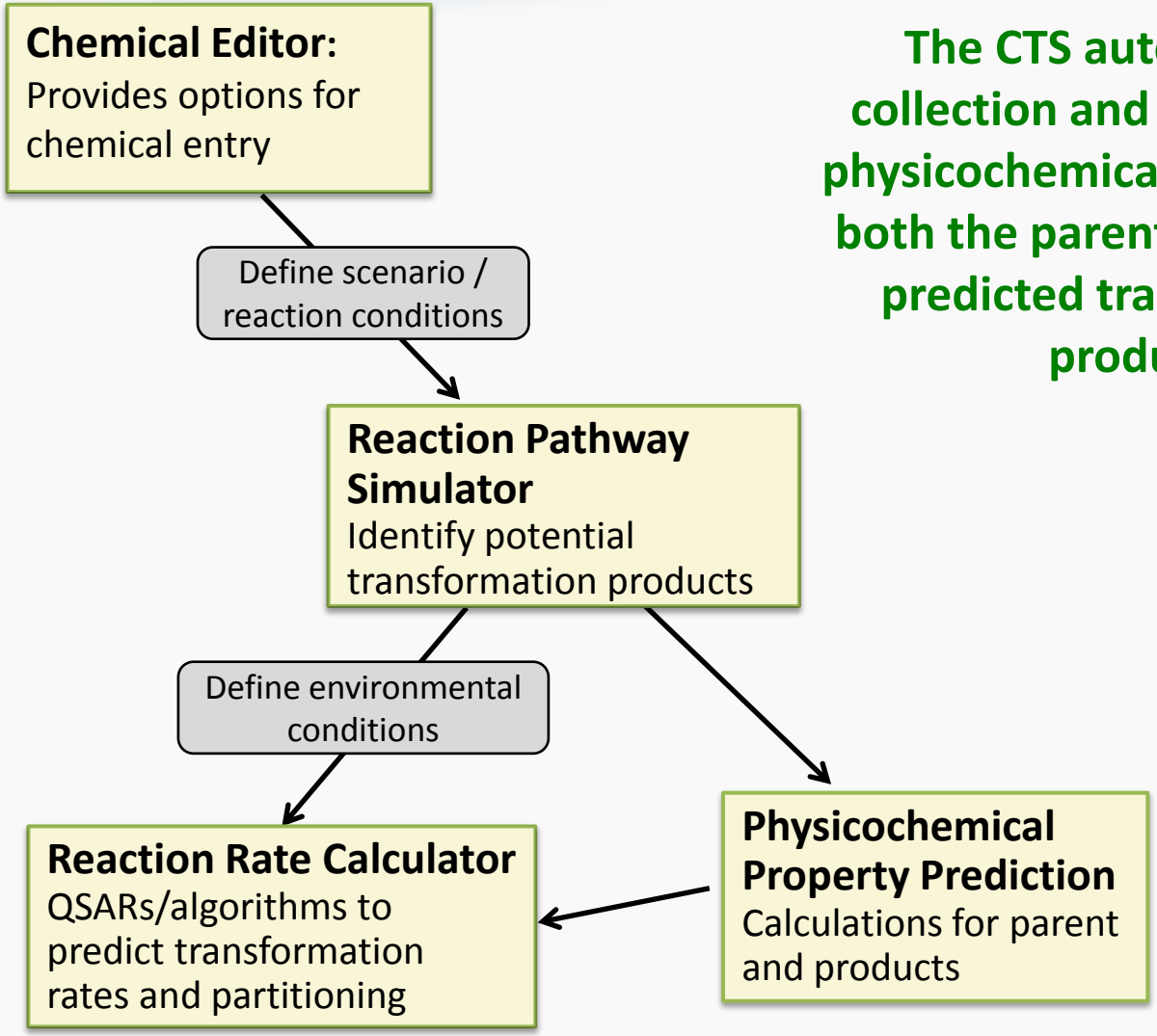
Chemical Transformation Simulator

A Web-Based System for Predicting Transformation Pathways and Physicochemical Properties of Organic Chemicals

Role in Environmental Modeling

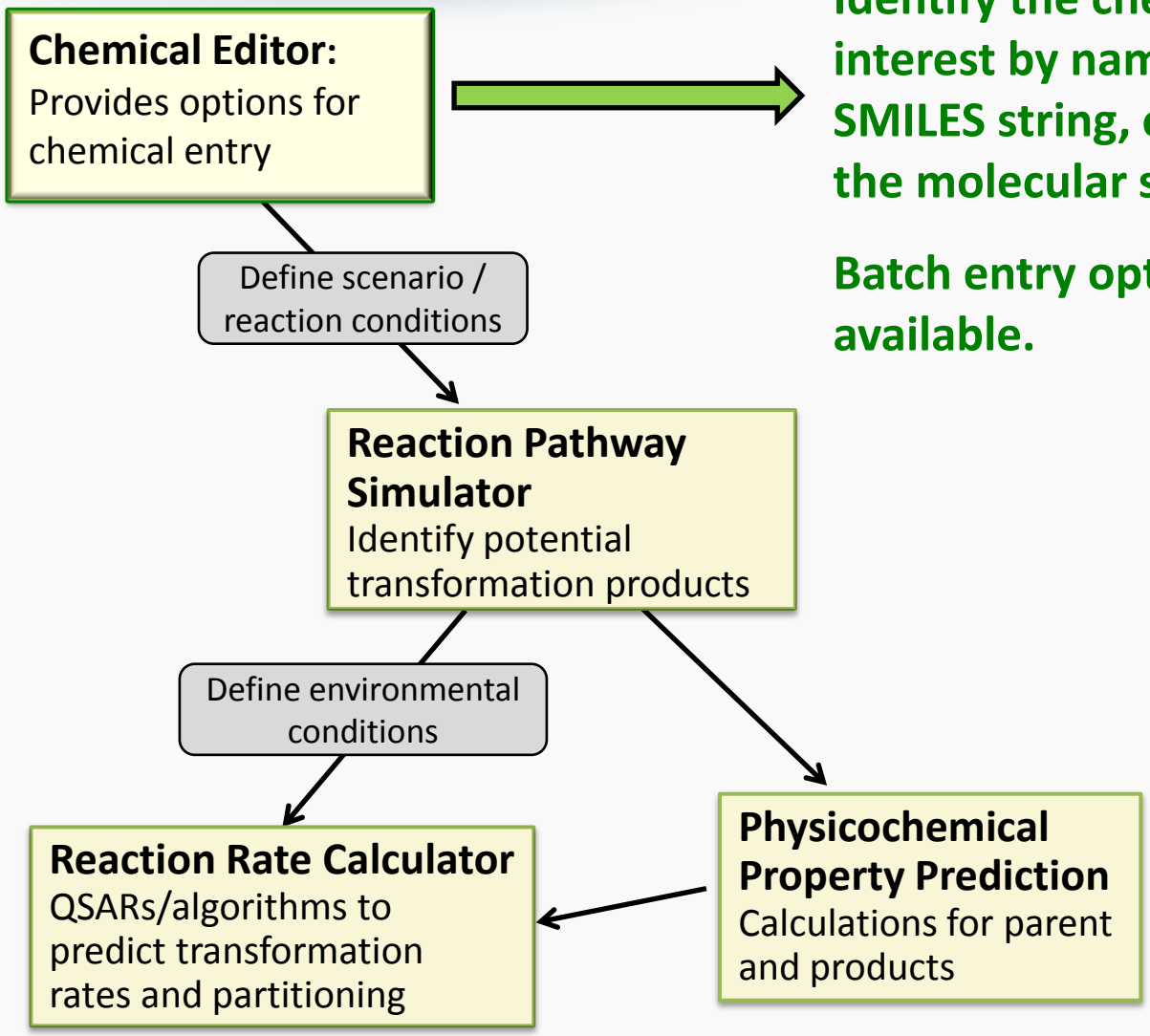
- Screening tool for identifying likely transformation products in the environment
- Parameterization tool for environmental fate and transport models
- Analytical tool to compare physicochemical properties of a chemical of interest to other chemicals and to assess uncertainty in estimated property values

General Workflow



The CTS automates the collection and calculation of physicochemical properties for both the parent chemical and predicted transformation products.

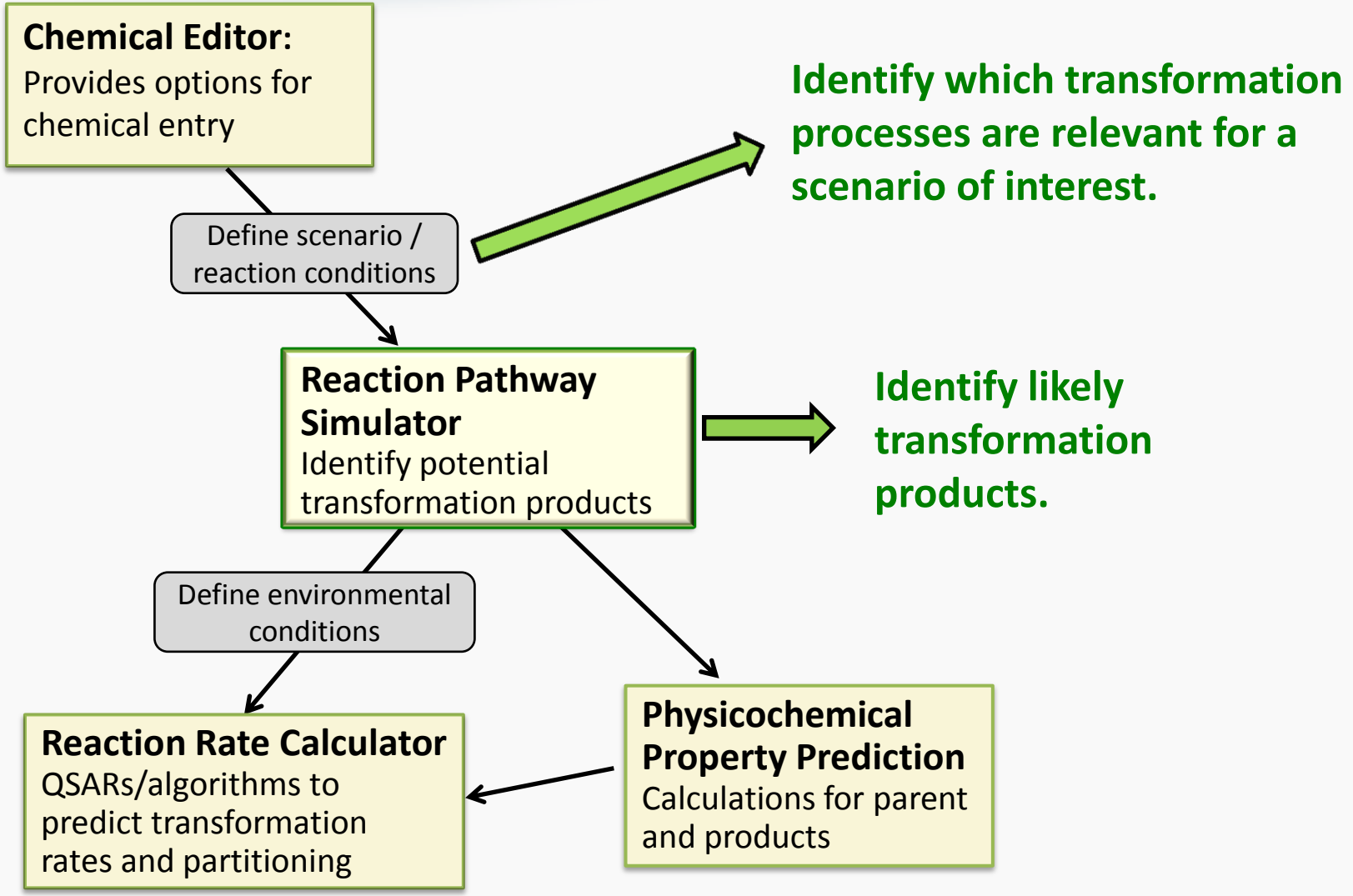
Steps in the Workflow



Identify the chemical of interest by name, CAS ID #, SMILES string, or by drawing the molecular structure.

Batch entry option also available.

Steps in the Workflow



Reaction Pathway Simulator

Reaction Library: A collection of reaction schemes associated with a particular transformation process

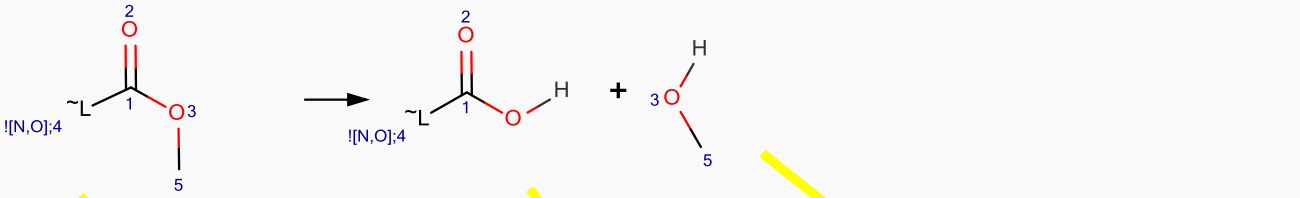
- Each scheme within a library is ranked according to likelihood (scale of 1 to 5)
- Database of observed transformation rates to support ranking of schemes and development of QSARs for rate prediction

Reaction Library	Status
Abiotic hydrolysis	Refinement and Testing
Abiotic reduction	Refinement and Testing
Aerobic biodegradation	Linkage to U. of Minn./EAWAG PPS
Anaerobic biodegradation	Under development
Photolysis	Under development
Mammalian metabolism	Library from ChemAxon

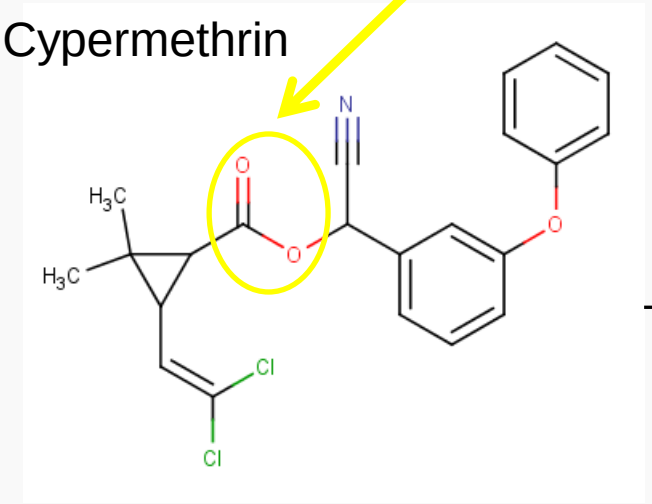
Reaction Pathway Simulator

Prediction of Transformation Products

Scheme for Carboxylic Acid Ester Hydrolysis

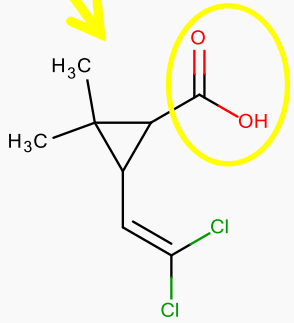


Cypermethrin



log Kow = 5.44

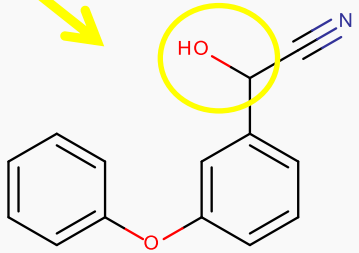
Oral rat LD_{50} = 0.14 mmol/kg



log Kow = 2.33

log D (pH 7) = -0.65

+

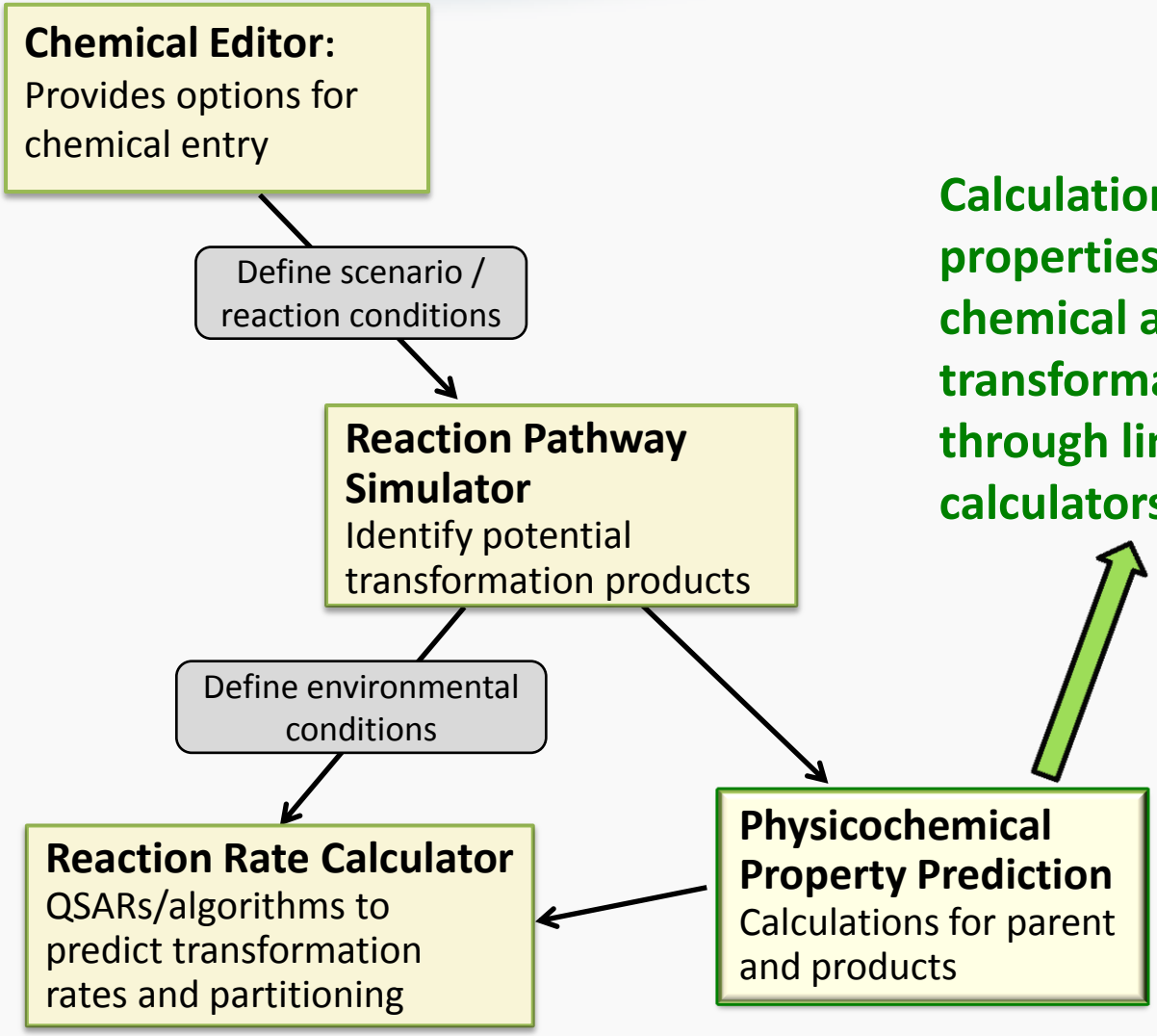


log Kow = 2.45

log D (pH 7) = 2.45

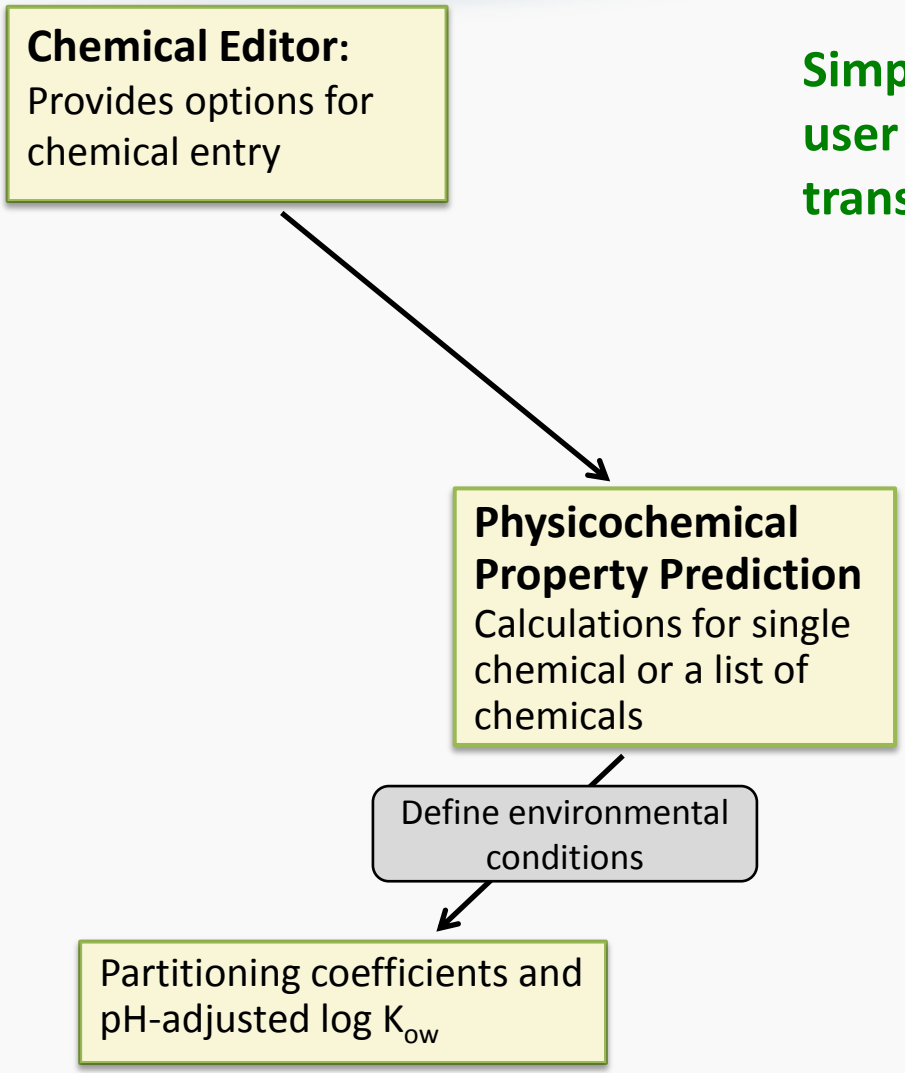
LD_{50} = 3.55 mmol/kg

Steps in the Workflow



Calculation of physicochemical properties for both the parent chemical and predicted transformation products through linkage to existing calculators.

Simplified Workflow



Simplified workflow if the user is not interested in transformation products

Physicochemical Property Prediction

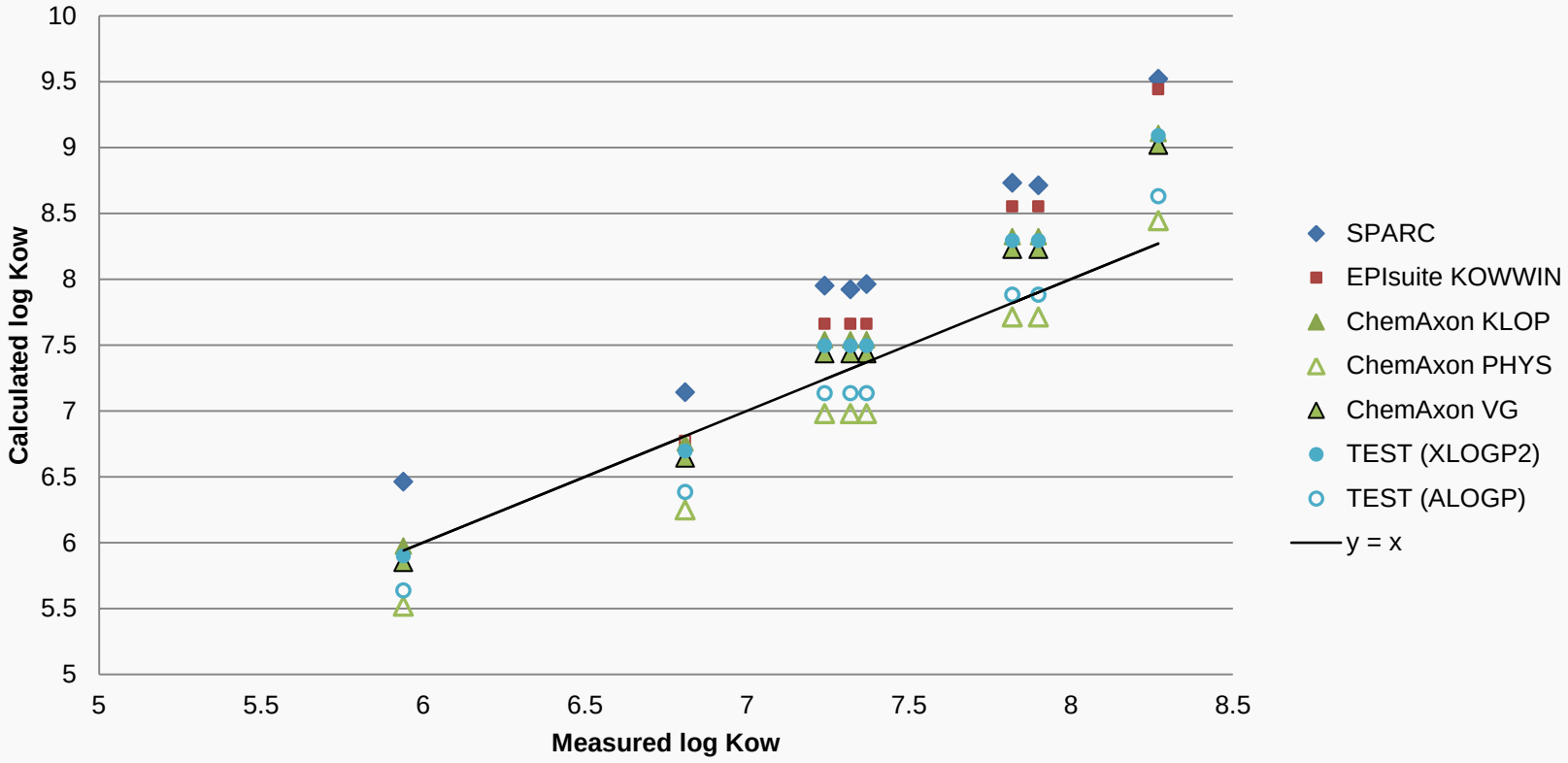
- Physicochemical properties are calculated by linking to existing calculators (ChemAxon plug-ins, EPI Suite, TEST)
  - Water solubility
  - Octanol-water partition coefficient (Kow)
  - pH-adjusted Kow
  - Organic carbon partition coefficient
  - Vapor pressure
  - Henry's Law constant
  - Ionization constants (pKa)
  - Diffusivity in water and air
  - Melting point & boiling point
- Many of these properties are needed to parameterize fate and transport models.
- Some of these properties are dependent on pH, temperature, etc.

Physicochemical Property Prediction

- **Consensus Approach**: Physicochemical property predictions are obtained from calculators that are based on different approaches
  - **ChemAxon**: Blend of mechanistic and QSAR-based approaches
  - **Toxicity Estimation Software Tool (TEST)**: QSAR-based approach using structural, topological and electrostatic descriptors
  - **EPI Suite**: Fragment-based approach
  - **SPARC** (behind EPA firewall): Mechanistic approach

Physicochemical Property Prediction

Consensus Approach: Comparison of calculated vs. measured log Kow values for a set of polybrominated diphenyl ethers (PDBEs)



Measured values from Braekevelt et al (2003)

Physicochemical Property Prediction

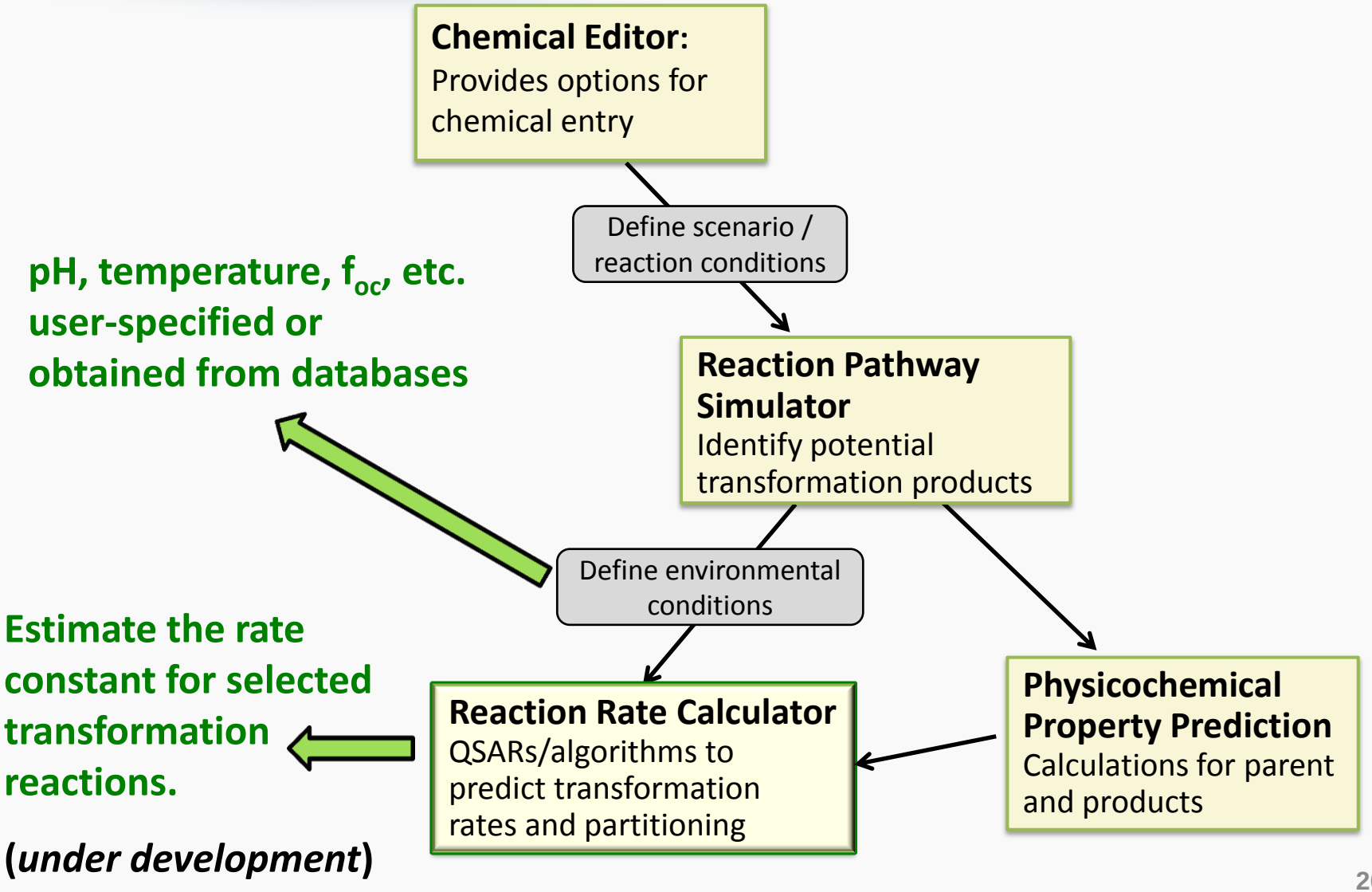
Consensus Approach: Comparison of RMSE for calculated vs. measured log Kow values for chemicals of low solubility

Chemical Class	EPI suite KOWWIN	SPARC	ChemAx VG	ChemAx KLOP	ChemAx PHYS	TEST ALOGP	TEST XLOGP2	Average of calculated K_{ow} values
PBDEs	0.58	0.76	0.34	0.40	0.34	0.25	0.38	0.43
Phthalate esters	0.78	0.40	0.48	0.79	0.54	0.53	1.17	0.81
PCBs	0.76	0.87	0.57	0.72	0.71	0.73	0.77	0.73
Fused ring structures	0.29	0.41	0.74	0.85	0.93	1.24	0.36	0.31
Others	0.31	0.86	1.51	0.87	0.61	1.19	1.32	0.53
ALL	0.58	0.74	0.94	0.75	0.64	0.90	0.96	0.60

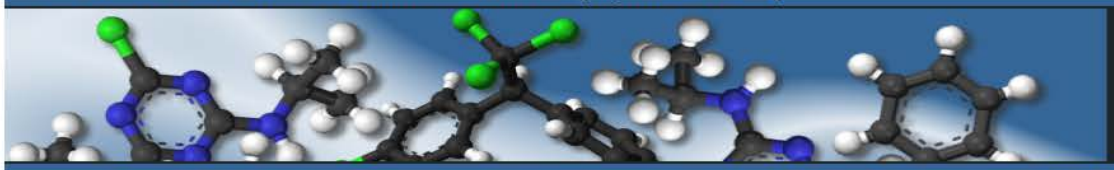
Physicochemical Property Prediction

- **Structure-Searchable Database**: Compilation of predicted physicochemical property values from all calculators
  - Measured values are included when available
  - Allows for comparison of structurally similar chemicals
- **Model parameterization**
  - Pull model input parameters from structure-searchable database
  - Calculations available through web services

Steps in the Workflow



cts: Chemical Transformation Simulator (alpha version)



Cloud-based [illegible] simulation

Contact Us

Execute CTS Workflow

- Calculate Chemical Speciation
- Calculate p-Chem Properties
- Generate Transformation Products

Access Databases

- FIFRA Chemicals
- Flame Retardants

Reaction Library Databases

- Abiotic Hydrolysis
- Abiotic Reduction
- Mammalian Metabolism

This web site is under development. It is available for the purposes of receiving feedback and quality assurance from personnel in the EPA Office of Chemical Safety and Pollution Prevention and from interested members of the ecological risk assessment community. Ecological risk calculations contained here should be used for no purpose other than quality assurance and peer review of the presented web applications.

The Chemical Transformation Simulator (CTS) provides the calculated physico-chemical properties of the parent chemical and transformation products, which are predicted as a function of the reaction system of interest. This is accomplished through the integration of cheminformatics applications for the encoding of process science underlying transformation pathways, computational chemistry tools for the calculation of physico-chemical properties, and software technologies that provide access to on-line databases for environmental descriptors required for estimating environmental concentrations.

The CTS consists of 6 modules, the selection and order of execution of which is based on the user's choice of one of three available workflows:

Chemical Editor (CE): Provides options for chemical entry, as well as the chemical speciation of the parent chemical

Physicochemical Properties Calculator (PPC): Calculates p-chem properties for the parent chemical and predicted transformation products based on the executions of multiple p-chem calculators

Reaction Pathway Simulator (RPS): Generates potential transformation products based on user-specified reaction conditions

Structure-based Database (SBD): Populated with calculated and measured physico-chemical properties of parent and potential transformation products

Earth Systems Model (ESM): Provides data mining abilities for environmental descriptors such as pH and temperature

Reaction Rate Calculator (RRC): Calculates transformation products based on the parameritization and execution of QSARs and Algorithms

P-Chem Calculators

- EPI Suite
- SPARC
- ChemAxon
- TEST

Chemical Information

- ChemSpider
- PubChem
- ChmIDplus
- DSSTox
- ChemLook

Chemical Regulation Programs

- TSCA
- FIFRA

Status

- Beta-version of the Chemical Transformation Simulator available at end of FY15
  - Cloud-based web application
  - Physicochemical properties for both parent and transformation products
  - Predicted transformation products for abiotic hydrolysis, abiotic reduction, aerobic biodegradation and mammalian metabolism

Sustainable Chemistry

Mace Barron, NHEERL
Dalizza Colón, NERL
Mike Gonzalez, NRMRL
Said Hilal, NERL
Jack Jones, NERL
John Leazer, NRMRL
*Todd Martin, NRMRL
Ann Richard, NCCT
*Caroline Stevens, NERL
Eric Weber, NERL

*co-leads

CTS Development Team

Process Scientists

Eric Weber (Lead)
Caroline Stevens
Said Hilal
Dalizza Colón
Jack Jones
Marcy Card (postdoc)
Jay Patel (student)
Meredith Martin (student)

Software Engineers/ Multimedia Modelers

Kurt Wolfe
Rajbir Parmar
Mike Galvin
Gene Whelan
Tom Purucker
Nick Pope (student)
Mitch Pelton (PNNL)
Pavan Gupta (CSC)