Development of *In-Silico* Tools at OFAS CFSAN FDA

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Outline

- Chemical Evaluation and Risk Estimation System (CERES)
- QSAR model development for food ingredients
- Evaluation of *in vitro* data for applications to food ingredient assessment

Chemical Evaluation and Risk Estimation System (CERES)

- Created to address technical challenges in food ingredient evaluation processes in the Office of Food Additive Safety (OFAS)
- Designed to be a knowledgebase of chemicals regulated by CFSAN
  - Most CFSAN compounds in CERES are food chemicals
    - Priority-Based Assessment of Food Additives (PAFA) Database
    - Food Application Regulatory Management (FARM) System
  - Incorporation of cosmetics compounds
- Designed to be expandable
- Designed to provide cheminformatics capabilities
- Releases: 1.0 (2012), 1.1 (2014), 2.0 (August 2015)

Priority-Based Assessment of Food Additives (PAFA) Database

- US FDA developed legacy database that contains oral toxicity information on ~1700 direct food additives regulated in the US since 1970

- Information content in PAFA records:
  - Regulatory Information:
    - Code of Federal Regulations
  - Chemical Information
    - Chemical names, CASRN, the annual usage in food, estimated daily U.S. human intake and the Joint Committee on Food Additives Allowable Daily Intake values, the FDA Redbook structure categories of the chemicals, and their technical effects
  - Toxicology Information:
    - Summary level *in vivo* and *in vitro* assay data which include species/strain, toxicological effects and their sites, highest/lowest no effect level per study, the lowest doses, and citation, etc.

Priority-Based Assessment of Food Additives Database of the U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition, Environmental Health Perspectives, Vol. 96. pp. 85-89, 1991

Food Application Regulatory Management (FARM) System

- OFAS submission repository and workflow system
- Submissions typically contain chemistry, toxicology, environmental, nutritional, microbiological, and other data relevant to supporting the safety review
- Data abstracted into CERES:
  - Chemical information: chemical name and CASRN
  - Regulatory information:
    - Submission title, submission type, received/completed dates, status, etc.
  - Toxicology information:
    - Full *in vivo* and *in vitro* study reports, literature references, etc.

Summary of Toxicity Studies in CERES

Data Sources	Numbers of Toxicity Studies
PAFA Database	12198
Original studies from FARM	813
Oral Repeat Dose Toxicity Database (oRepeatToxDB)*	341

*Obtained through collaboration with COSMetics to Optimise Safety (COSMOS)

CERES Toxicity Information Domain

- 32 toxicity assays
  - *In vitro* assays:
    - Bacterial mutagenesis, cell transformation, cytotoxicity, DNA covalent binding, DNA damage/repair, *in vitro* chromosome aberration, *in vitro* micronucleus, in vitro mammalian mutagenesis, recombination/gene-conversion, etc.
  - *In vivo* assays:
    - Acute, chronic, sub-chronic, reproductive, developmental, reproductive-developmental, multi-generation reproductive, target organ toxicity, carcinogenicity, neurotoxicity, immuno-toxicology, *in vivo* chromosome aberration, *in vivo* mammalian mutagenesis, *in vivo* non-mammalian mutagenesis, *in vivo* micronucleus, short-term toxicity
- Assay data in CERES is linked to:
  - Chemical data: CRS-ID
  - Study data: title, background, test/study calls, comments, etc.
  - Test data: species/strain, sex, dose, toxicity values, etc.

CERES Chemical Information Domain

- 88674 compounds
- Chemical information:
  - Chemical identifiers
    - CERES-IDs, CASRN, names, DSSTox GSIDs, etc.
  - Chemical information sources
    - CFSAN Thesaurus, DSSTox, Chemical Abstract Service (CAS), COSING, etc.
  - Use types:
    - Pigments, coloring agents, extracts, foam boosting, etc.
  - Use functions
    - Food contact substance, food additive, flavor, colorants, etc.
  - Cumulative Estimated Daily Intake (CEDI) database
- Chemical Structures: SciFinder, Chemical Abstract Service, US EPA DSSTox, Altamira
- CERES chemical data linked to:
  - Toxicity and regulatory data (submission type, submission number, links to original submissions, etc.)

Chemical-Centric Information View

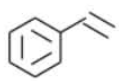
FDA CFSAN CERES **Compound Information**

Home Help Patra Volarath

CERES ID CRS-1298
Preferred name STYRENE
CAS Registry Number 100-42-5

Actions
Generate Report
Perform Similarity Search
Predict Toxicity
Export Molecule

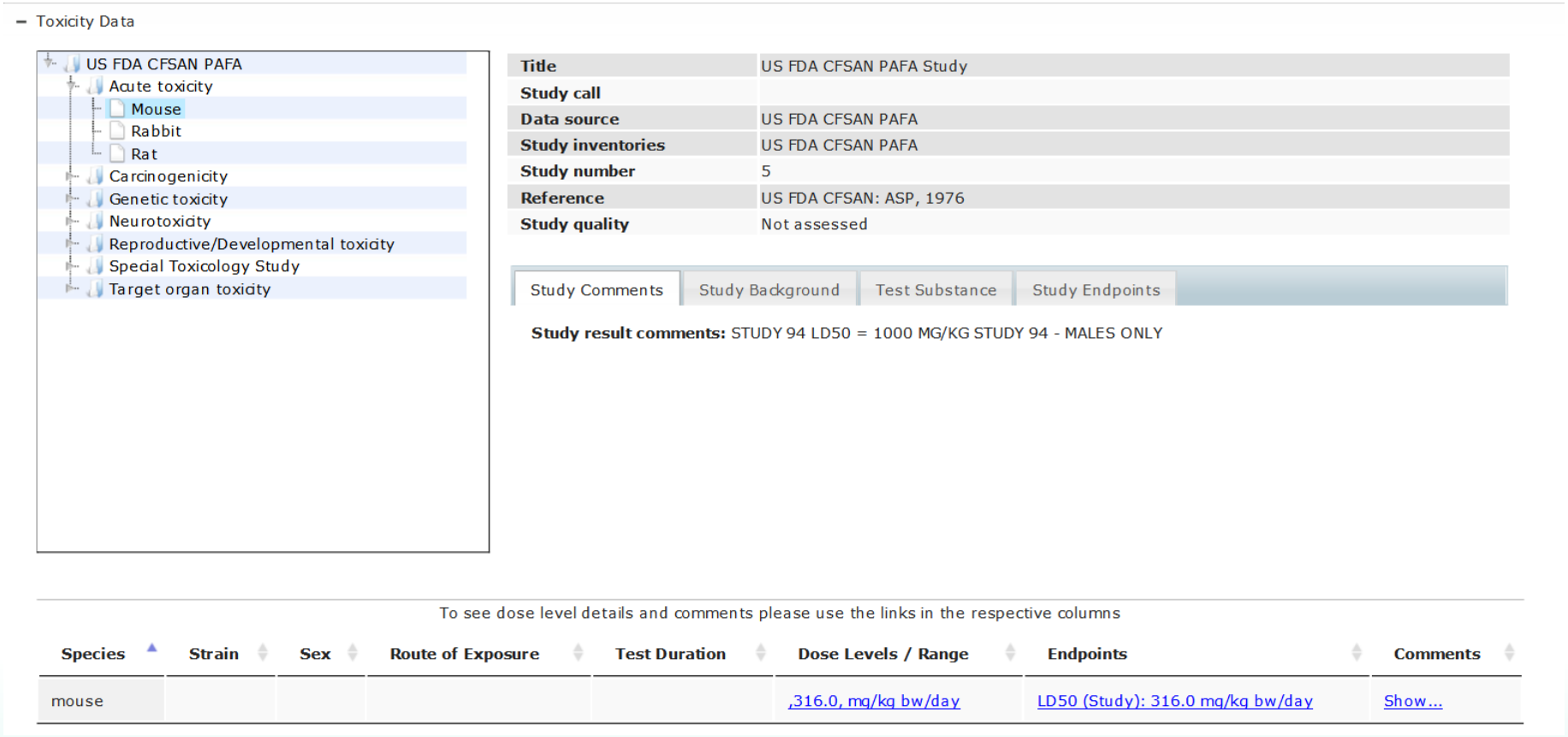
Structure #1



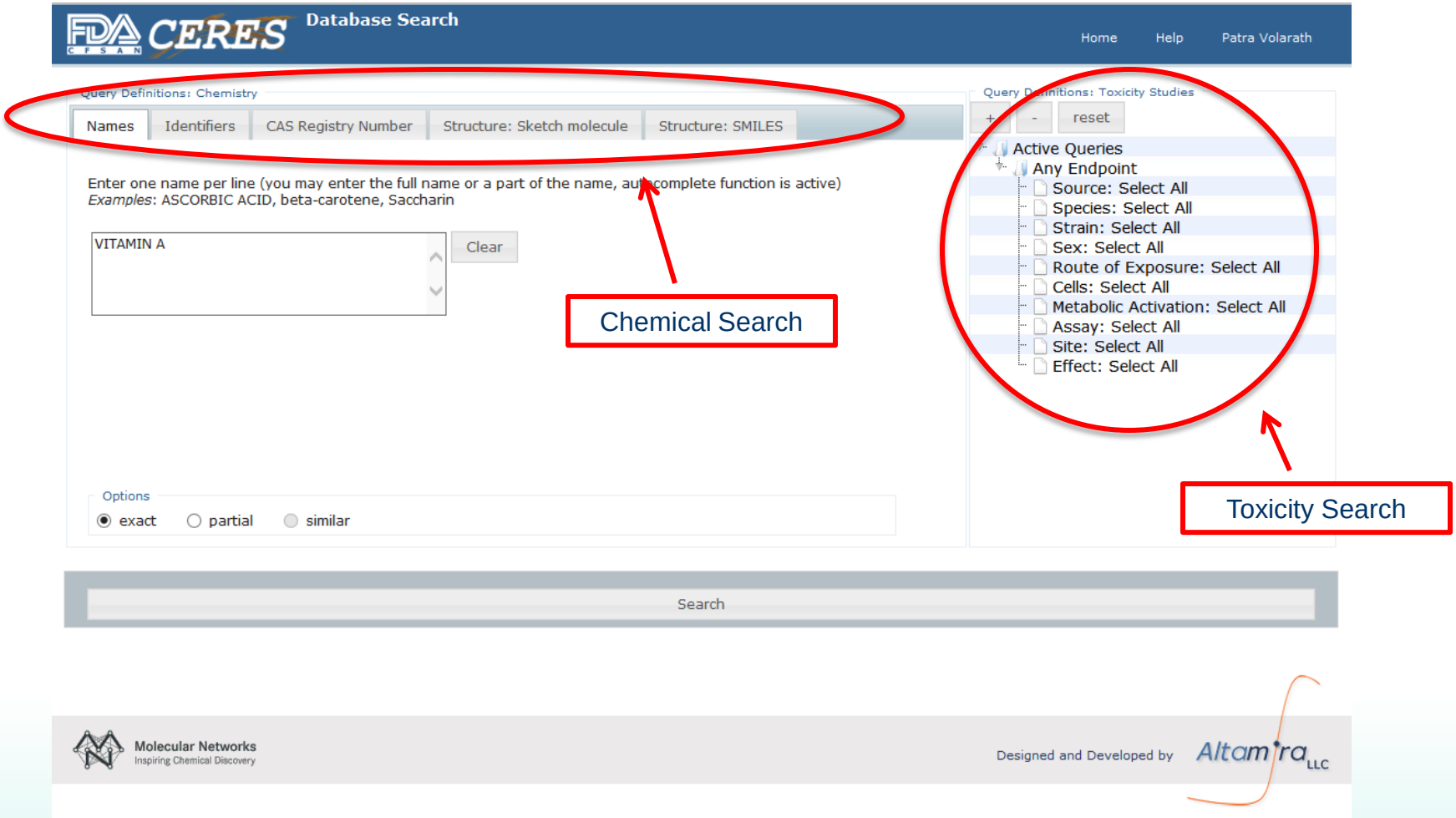
Stereochemistry	unassigned
Double Bond Geometry	unassigned
Structure Source	CAS
Structure Quality	High
Structure Representation	actual

+ IDs and Names
+ Compound Annotations
+ Regulatory Information
+ PAFA Chemical Information
+ Daily Intake (CEDI/ADI Database)
+ Toxicity Data

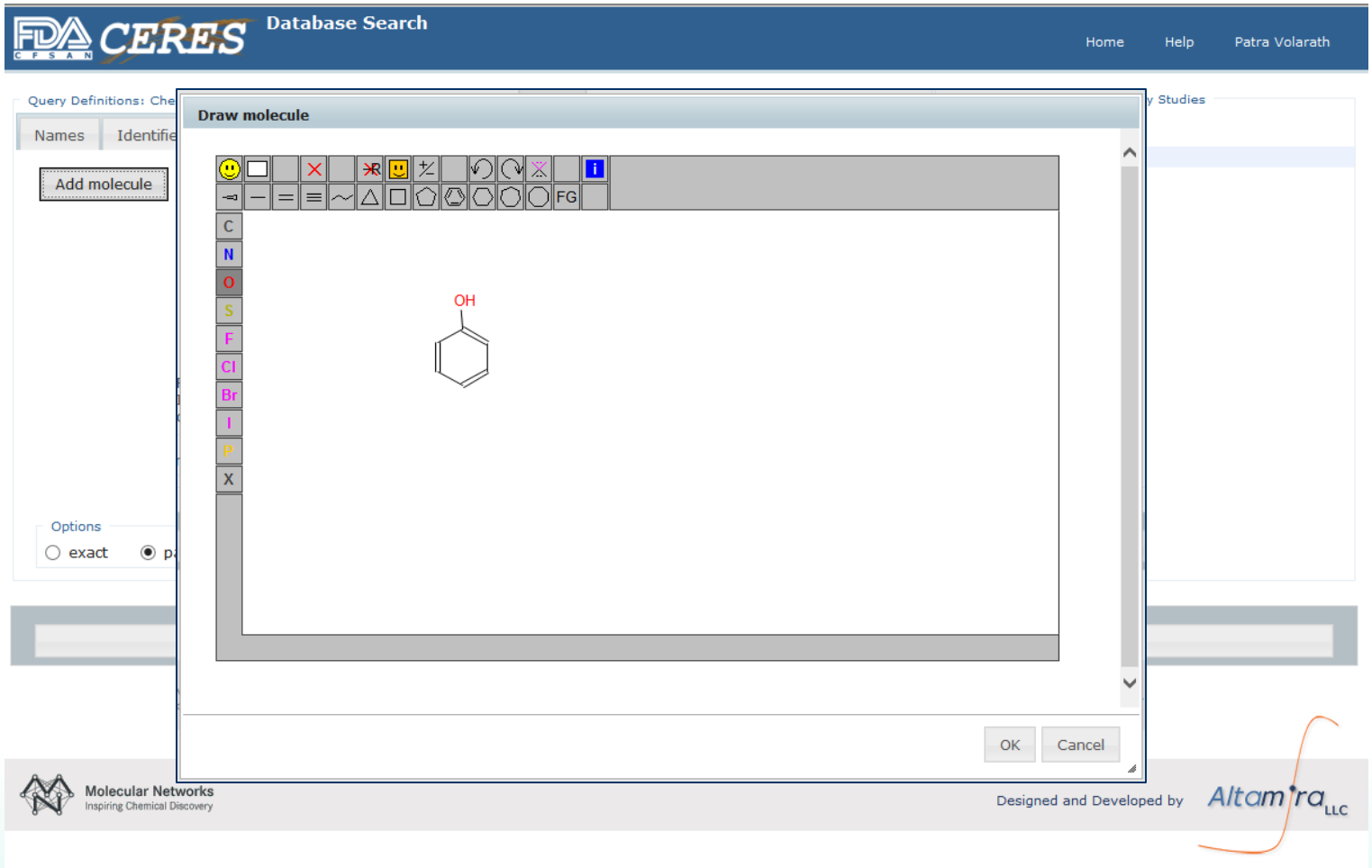
Expanded Toxicity Data View



User Interaction and Search Capabilities



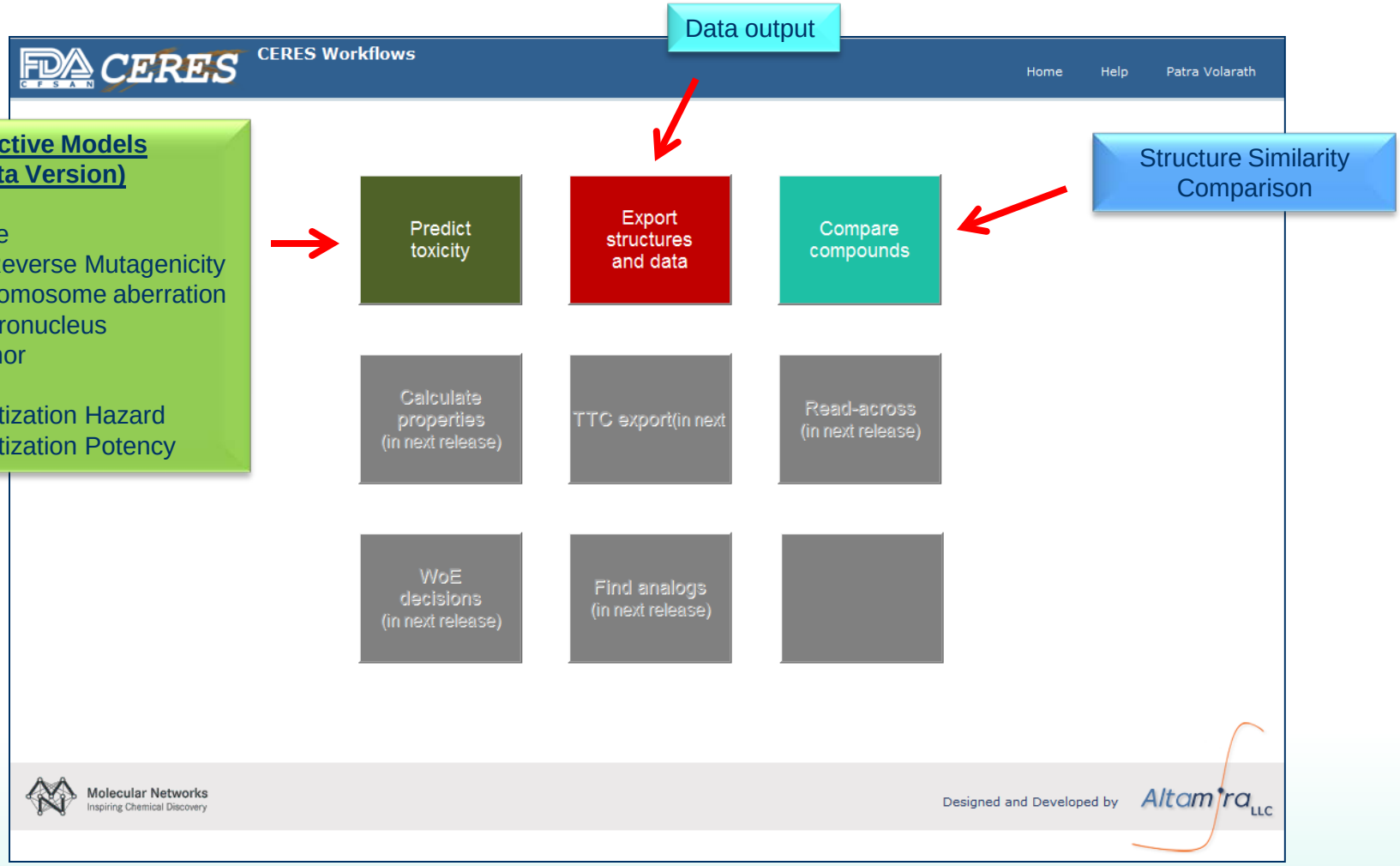
Structure-Based Search Capability



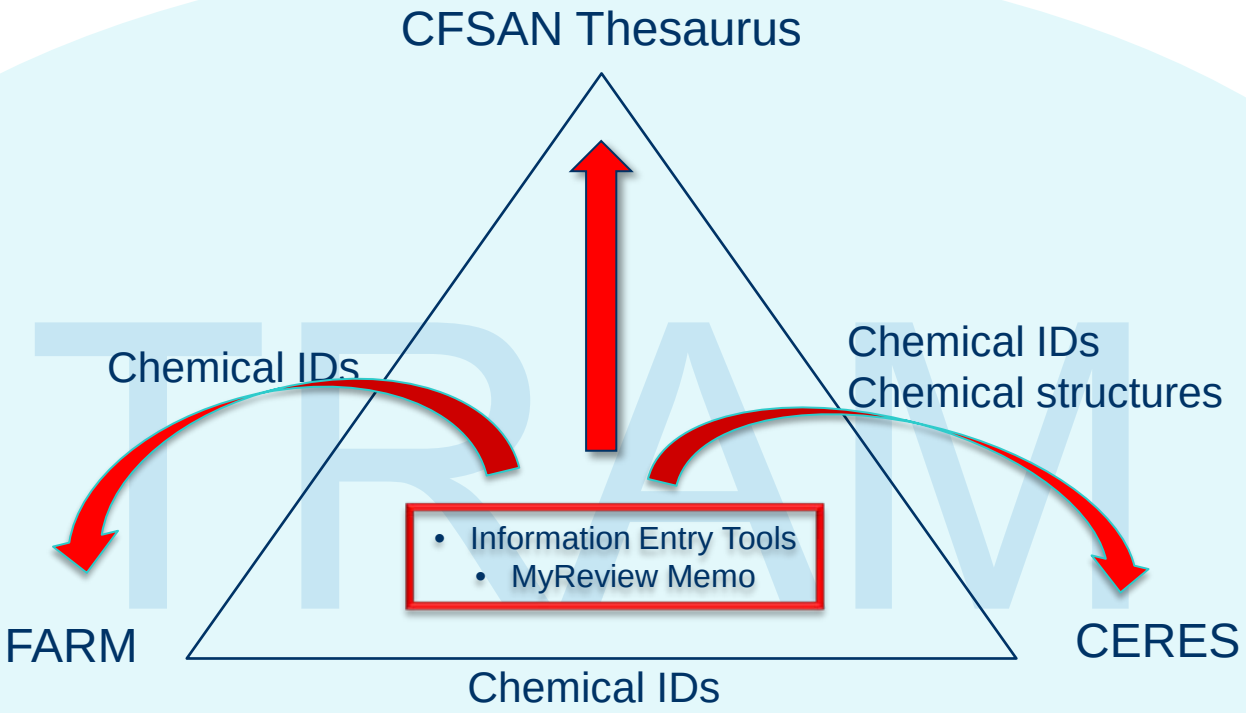
Informatics Workflows

Predictive Models (Beta Version)

- Cleft Palate
- Bacterial Reverse Mutagenicity
- In vitro chromosome aberration
- In vivo micronucleus
- Mouse tumor
- Rat tumor
- Skin Sensitization Hazard
- Skin Sensitization Potency

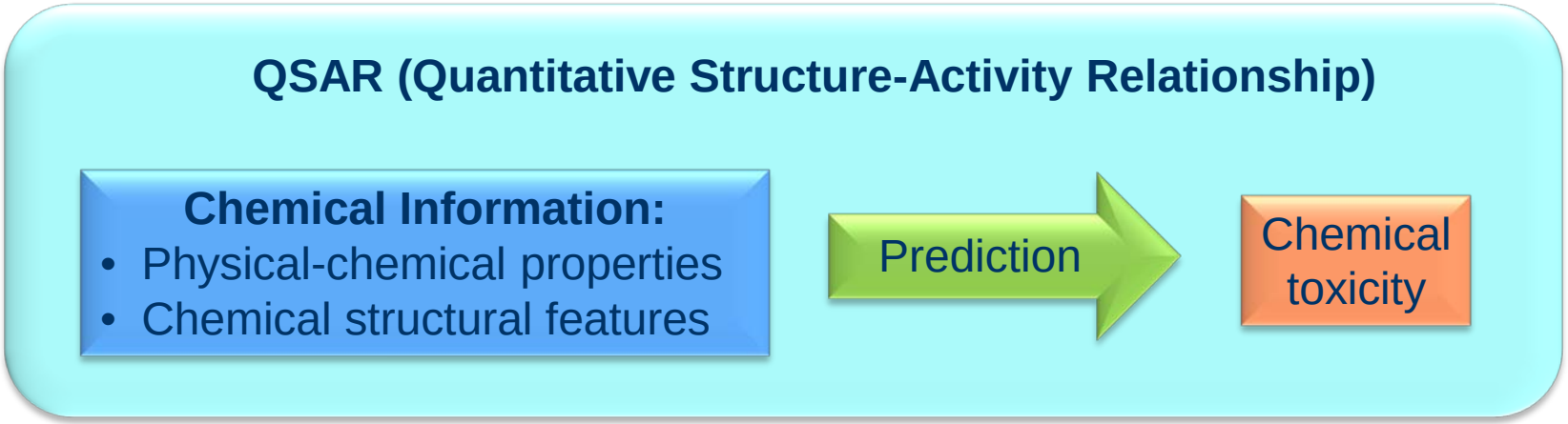


CERES Project Current and Future Status: Toxicity Report & Analysis Management (TRAM) System



CERES Team Lead: Dr. Kirk Arvidson, kirk.arvidson@fda.hhs.gov

QSAR Model Development for Food Ingredients



- OFAS scientists/reviewers use QSAR models to:
  - predict chemicals' toxicity outcomes when there is no or little toxicity data available
  - check notifiers' safety claims on submissions
- Challenges:
  - Predictions are only as accurate as the data in the training set
  - Commercial QSAR models may be too generic
- Need: customized QSAR models for food ingredients

Predictive Models for Food Ingredients

QSAR Models in CERES 2.0 (Beta)*
Cleft Palate
Bacterial Reverse Mutagenicity
In vitro chromosome aberration
In vivo micronucleus
Mouse tumor
Rat tumor
Skin Sensitization Hazard
Skin Sensitization Potency

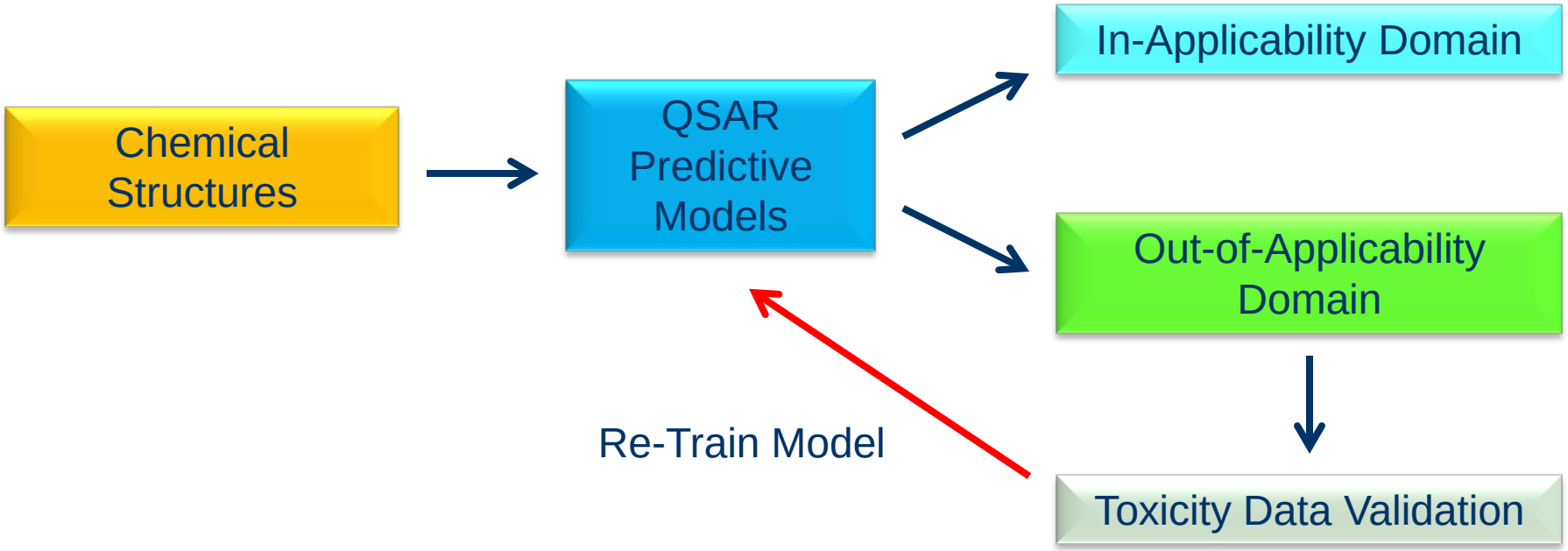
*Collaboration with Altamira/Molecular Network

How applicable are these models to food ingredients?

Public Food Ingredient Databases

Food Ingredient Inventories	Abbreviations	# Records in Datasets
Everything Added to Food in the United States	EAFUS	3968
Flavor and Extract Manufacturers Association	FEMA	2758
Generally Recognized as Safe	GRAS	572
Indirect Food Additives	Indirect	3237
Priority-Based Assessment of Food Additives	PAFA	7202
Food Contact Substances	FCS	1155
Select Committee on GRAS Substances	SCOGS	373

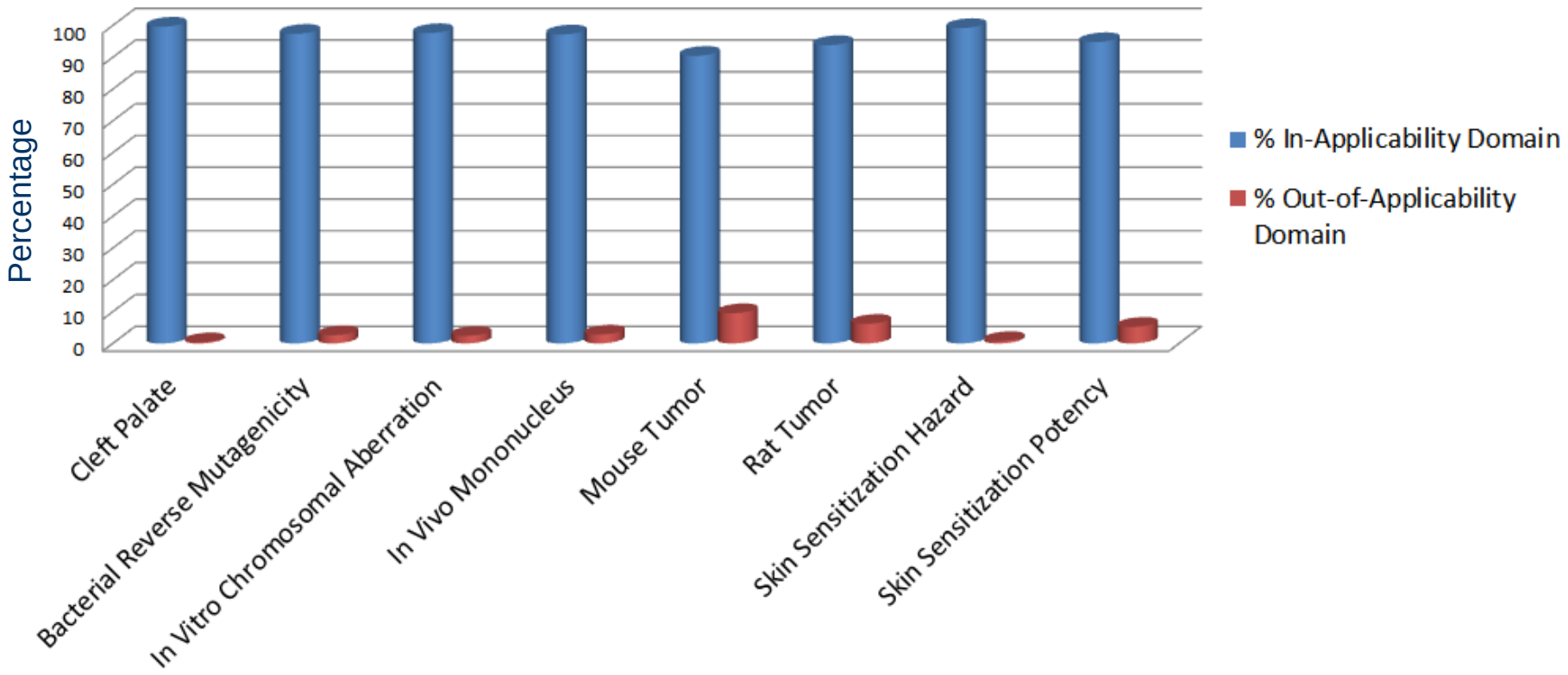
Food Ingredient QSAR Model Development Workflow



Advantages:

- Better predictive models for food ingredients
- Provide transparency

Applicability Domain Coverage



"Evaluation of the chemical inventories in the US FDA CFSAN for human health endpoints using a toxicity prediction system", SOT 2016, New Orleans, LA

Evaluation of *In Vitro* Data for Food Ingredients: ToxCast Phase II

- Released: December 2013
- Data package included:
  - Chemical structures/information for ToxCast/Tox21 compounds
  - 1045 *In vivo* toxicity outcomes
  - 711 high-throughput *in vitro* assays

ToxCast Assay Descriptions*

Assay Descriptions	Numbers of Assays
Cell Proliferation	2
Regulation of transcription factor activity	164
Effects of chemicals on toxicity biomarkers	60
Inhibition/activation of enzymatic activities	420
Binding Reporter Dimerization	18
Steroid-nuclear receptor interaction (Tox21)	47
Total Assays	**711**

*Kavlock, R., et al, Update on EPA's ToxCast Program: Providing High Throughput Decision Support Tools for Chemcial Risk Management, Chemical Research in Toxicology, 2012, 25, 1287-1302
A Comparison of ToxCast in Vitro Testing with In Vivo Endpoints for Endocrine and Developmental Toxicities: A Case Study Using Endosulfan and Methidathion, Poster presentation by CalEPA

Goals:
1. Determine relationships between the traditional toxicity assays in CERES and ToxCast high-throughput assays
2. Bring knowledge derived from ToxCast/Tox21 screening assays to OFAS review scientists

ToxCast/Tox21 Chemical Coverage

ToxCast:

Unique CERES Compounds	Total *ToxCast* Compounds*	# Overlapped Chemicals	% *ToxCast* Overlap
88674	1058	907	85.73

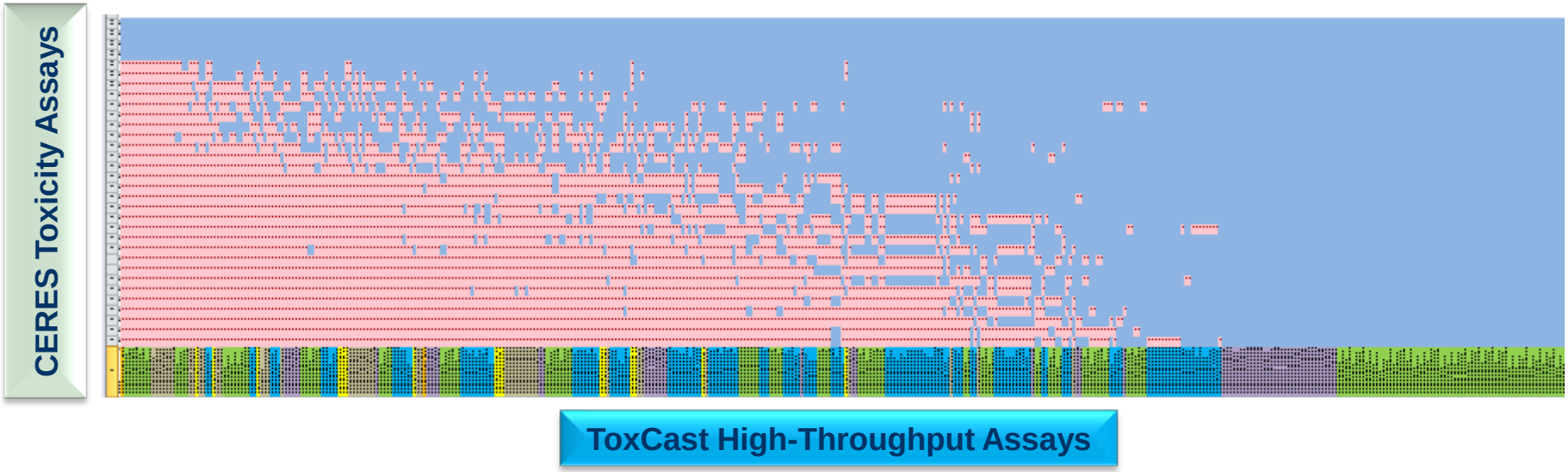
*Excluded E1k chemicals that are not in ToxCast

Tox21:

Unique CERES Compounds	Total *Tox21* Compounds	# Overlapped Chemicals	% *Tox21* Overlap
88674	8454	7849	92.84

- ToxCast = a chemical prioritization program initiated by the US EPA
- Tox21 = a collaborative research between US FDA, US EPA, NTP (National Toxicology Program), NCATS (National Center for Advancing Translational Sciences)

Overlap of ToxCast HTP and CERES Toxicity Assays



Pink = ***presence*** of compounds in ToxCast and CERES toxicity assays
Blue = ***absence*** of compounds in ToxCast and CERES toxicity assays

Summary

- Chemical Evaluation and Risk Estimation System (CERES)
  - Continue harvesting more data to enhance CERES knowledgebase
  - Expand CERES chemical library to cover other CFSAN chemicals of interest
  - Increase informatics capability
- QSAR model development
  - Improve models' prediction performance for food ingredients
  - Expand models' applicability to new chemicals
- Evaluation of *in vitro* data for applications to food ingredient assessment
  - Evaluate relationships between the ToxCast HTP data and traditional toxicity assay data in CERES
  - Bring the knowledge into CERES to make it available to the reviewers in OFAS

More Information on CERES

- CERES Team Lead: Dr. Kirk Arvidson, kirk.arvidson@fda.hhs.gov

- Publications:
  - Arvidson K, McCarthy A, Hristozov D, Yang C, Cronin MT (2014) Applying Databases and Tools from COSMOS to the Scientific Needs of US FDA's CERES Project. SOT 53rd Annual Meeting, 24–27 March 2014, Phoenix, Arizona, USA

  - Yang C, Arvidson K, Detroyer A, Mostrag-Szlichtying A, Rathman JF, Ringeissen S, Worth AP (2012) A Mode-of-Action-based QSAR approach: skin irritation models implemented in CERES (Chemical Evaluation and Risk Estimation System). 15th International Workshop on Quantitative Structure-Activity Relationships (QSAR2012), 18-22 June 2012, Tallinn, Estonia

Acknowledgements

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