Appendix A, Part 2: CSS Scientific Portfolio Overview

The following are anticipated products responsive to the research objectives and outputs outlined in the CSS FY 2019 – FY 2022 Strategic Research Action Plan (StRAP). Products and product types may change as new scientific findings emerge. Completion of outputs and products is contingent on appropriate resources being available. Product list updated as of January 2021.

Gray highlighting indicates product has been completed.

Research Area 1: High-Throughput Toxicology (HTT)		
Output 1.1: Develop assays, datasets, data analyses, and models to inform frameworks that support rapid, cost-effective approaches for screening large inventories of chemicals for bioactivity in the estrogen, androgen, thyroid, and/or steroidogenesis pathways		
Product Number	**Product Title**	**Product Type**
1.1.1	Optimization of a high-throughput H295R assay for androgen and estrogen steroidogenesis screening	Dataset
1.1.2	Refinement of a model to predict androgen receptor activity using ToxCast data	Publication
1.1.3	Refinement of models to evaluate steroidogenesis disruptors using ToxCast data	Publication
1.1.4	Synthesis of computational tools and ToxCast data across battery of thyroid-related in vitro assays to predict thyroid-active chemicals in aquatic vertebrates	Publication
1.1.5	Expansion of thyroid-related in vitro assay battery: development of screening assay for human iodotyrosine deiodinase (IYD) inhibition	Publication
1.1.6	Development of orthogonal thyroid-related in vitro assay for amphibian deiodinase inhibition and analysis of chemical potency concordance with human deiodinase assays	Publication
1.1.7	In vitro chemical screening for thyroid-related sodium-iodide symporter (NIS) inhibition using orthogonal assay systems and subsequent quantitative structure activity relationship (QSAR) modeling	Publication
Output 1.2: Develop, evaluate, apply, and interpret a developmental neurotoxicity (DNT) battery of assays to reduce uncertainties in chemical safety evaluations		
1.2.1	Behavioral screen for developmental neurotoxicity in zebrafish	Publication
1.2.2	Evaluation of a battery of in vitro developmental neurotoxicty (DNT) new approach methods (NAMs)	Publication
1.2.3	Expanded chemical space for developmental neurotoxicty (DNT) new approach methods (NAMs)	Publication
1.2.4	Tools for translation and accessibility of Developmental Neurotoxicty (DNT) New Approach Methods (NAMs)	Dataset

Output 1.3: Develop and apply medium-to high-throughput, transferrable methods to test and deliver novel hazard data on methodologically challenging chemical classes, such as volatile and non-dimethylsulfoxide (DMSO)-soluble chemicals		
1.3.1	Use in-vitro assessments to identify irritants/chemicals with portal of entry effects and differentiate them from systemic toxicants following simulated inhalation exposure	Publication
1.3.2	Development and application of organotypic in vitro airway models for medium- to high-throughput testing of chronic/sub-chronic toxicity of inhaled chemicals	Publication
1.3.4	Methods development for high-throughput screening of water-soluble chemicals	Publication
Output 1.4: Develop and apply methods to advance a tiered, high-throughput toxicity testing strategy including high-throughput and high-content methods (e.g., transcriptomics, phenotypic profiling, and other methods) that address key information needs of assessments		
1.4.1	High-throughput screening of environmental chemicals for bioactivity and molecular target identification using gene expression profiling	Publication
1.4.2	High-throughput screening of environmental chemicals for bioactivity and characterization of cellular effects via in vitro cellular pathology	Publication
1.4.3	Confirmation of bioactivity screening results using targeted confirmation assays and systems models	Publication
Output 1.5: Develop and apply methods to incorporate endogenous and exogenous xenobiotic metabolism into high-throughput in vitro assays		
1.5.1	Application of the alginate immobilization of metabolic enzymes (AIME) method to incorporate hepatic metabolism into an Estrogen Receptor transactivation assay	Publication
1.5.2	Development of a bioprinting approach to adapt the alginate immobilization of metabolic enzymes metabolism method for high-throughput screening applications	Publication
1.5.3	Application of an mRNA transfection method to retrofit an estrogen receptor transactivation assay with metabolic competence	Publication
1.5.4	Metabolic augmentation of a genotoxicity assay	Publication
Output 1.6: Develop the Per- and Polyfluoroalkyl Substances (PFAS) screening library and deliver information from integrated exposure and effects studies		
1.6.1	Nuclear receptor and stress gene responses of a per- and polyfluoroalkyl substances (PFAS) library in HepG2 cells	Publication
1.6.2	In vitro screening of the PFAS library for thyroid disruption	Publication
1.6.3	Effects of diverse PFAS on the development of zebrafish embryos	Dataset
1.6.4	Effects of diverse PFAS on phenotypic screens for developmental neurotoxicity	Dataset
1.6.5	Effects of diverse PFAS on immunotoxicity endpoints	Publication
1.6.6	Bioactivity of PFAS chemicals as determined using gene expression and in vitro cellular pathology	Dataset

1.6.7	Perform subchronic mammalian toxicity testing on a subset of refined PFAS groupings with no existing in vivo toxicity studies to anchor read-across assessment of Tier 1 studies	Publication
1.6.8	High-throughput in vitro testing of 15 additional PFAS to fill data gaps and refine structural and mechanistic groupings	Dataset
1.6.9	Pilot studies to develop an Interim Transcriptomic Assessment Product (ITAP) for PFAS priorities	Internal Report
Output 1.7: Develop, evaluate, and apply non-mammalian high-throughput toxicity tests for priority endpoints and pathways in ecological species for ecological risk assessment		
1.7.1	Assay development for alternative species in high-throughput ecological toxicity testing	Publication
1.7.2	Government challenge to increase transcriptomic coverage representing pathways of ecotoxicological significance by developing next generation tools for ecological toxicity testing	Report
1.7.3	Transcriptomic analysis of ecological species and a demonstration of potential data use in ecological risk assessment decision contexts	Report
1.7.4	Case studies for developing novel physiological health endpoints in support of cross-species ecological risk assessments	Publication
1.7.5	Expand high-throughput transcriptomics-based toxicity testing of PFAS to fish, invertebrates, and/or algae/plants to increase taxonomic coverage	Publication
1.7.6	Zebrafish embryo/larval toxicity testing with PFAS to address uncertainties in transcriptomic point of departure estimates across species	Publication

Research Area 2: Rapid Exposure Modeling and Dosimetry (REMD)

Output 2.1: Collect and curate exposure factor-related data (behavior patterns, habits and practices, product composition, and monitoring data) from publicly available sources for use as inputs to models used in regulatory assessments of human or ecological risk

Product Number	Product Title	Product Type
2.1.1	Expanded chemical use data, including data on occupational use of chemicals	Database
2.1.2	Metrics of chemical storage near drinking water sources to support chemical prioritization	Dataset
2.1.3	Mining of consumer product and purchasing data to identify potential chemical co-exposures	Publication
2.1.4	Updated consumer product use patterns for model parameterization, including for susceptible populations and an expanded product scope	Database
2.1.5	New datasets of harmonized chemical monitoring data, including data extracted from the literature	Database
2.1.6	Automated standardized emission and waste inventories to support chemical exposure assessment	Database

Output 2.2: Develop consensus exposure models for various exposure pathways (e.g., consumer, occupational, ambient, indoor environment, and ecological scenarios) that enable high throughput exposure predictions for chemicals		
2.2.1	Evaluation data for human consensus exposure models: Estimated U.S. population chemical intake rates from biomonitoring data	Dataset
2.2.2	Evaluation data for human consensus exposure models: Estimated U.S. population chemical intake rates from biomonitoring data	Model
2.2.3	Supporting models for characterizing exposure pathways: Predictive models estimating release or emission of chemicals from consumer articles	Publication
2.2.4	Supporting models for characterizing exposure pathways: Machine learning classifiers for filling gaps in exposure data	Model
2.2.5	High-throughput exposure models for critical pathways: Implementation and parameterization of models for occupational exposure	Model
2.2.6	High-throughput exposure models for critical pathways: New and refined high-throughput models for consumer pathways	Model
2.2.7	Consensus Expocast/SEEM models: Consensus high throughput exposure predictions for surface water chemical concentrations	Dataset
2.2.8	Consensus Expocast/SEEM models: Refined consensus human exposure model updates to address key population demographics and reduce uncertainty through improved chemical release information	Dataset
2.2.9	Consensus Expocast/SEEM Models: Consensus high-throughput predictions for worker exposure	Dataset
2.2.10	Consensus Expocast/SEEM models: Consensus human exposure predictions leveraging new advances in model extrapolation and analytical monitoring	Dataset
2.2.11	Application of exposure NAMs: Implementation of exposure models and data for support of chemical decision-making workflows	Dataset
2.2.12	Application of exposure NAMs: Evaluation of in silico of NAMs for exposure against traditional exposure data	Publication
Output 2.3: Develop end-of-use models for tracking chemicals in waste streams and the subsequent environmental releases and worker exposures, including novel end-of-life scenarios based on chemical type and function		
2.3.1	A data engineering approach for tracking chemical releases in end-of-life generic scenarios	Publication
2.3.2	Understanding end-of-use U.S. industrial chemical release profiles using data analytics techniques	Publication
2.3.3	Data-driven model systems to estimate releases from chemical end-of-use generic scenarios	Publication

Output 2.4: Expand capabilities of generic scenario processes by minimizing development time and increasing the number of available scenarios. This includes developing models and tools for estimating common scenario needs, data, and methods for estimating new chemical applications, life cycle releases, and occupational exposure support		
2.4.1	Review of generic scenario modeling approaches to identify opportunities for high-throughput application	Publication
2.4.2	The use of data mining and machine learning for expedited generic scenario modeling	Publication
2.4.3	Application of rapid generic scenario modeling methods for high-throughput chemical assessment: A case study	Publication
2.4.4	Utilizing read across methods and computer simulation for rapid generic scenario development	Publication
Output 2.5: Develop methods, approaches, and frameworks to enable rapid exposure evaluations for PFAS chemicals		
2.5.1	Quantitative analytical method development and quality assessments of PFAS in biological samples	Publication
2.5.2	PFAS in vitro toxicokinetic data generation and application in physiologically-based toxicokinetic modeling and new approach methodology (NAM) frameworks	Dataset
2.5.3	Development of Non-Targeted Analysis (NTA) workflows to allow identification of novel PFAS	Publication
2.5.4	Characterization of PFAS emissions from consumer products	Publication
2.5.5	Bioaccessibility of PFAS sorbed to ingested soils and house dusts	Publication
2.5.6	Measurement of hepatic clearance and plasma protein binding to parameterize toxicokinetic models on 15 additional PFAS compounds to inform relevance to human doses	Publication
2.5.7	Measurement of renal and transporter activity on 150 PFAS to more accurately predict renal excretion and entero-hepatic recirculation to inform extrapolation from laboratory to human doses	Publication
Output 2.6: Further develop high-throughput toxicokinetic (HTTK) tools to support in vitro to in vivo extrapolation. Tools to be developed include those needed to address current sources of uncertainty, challenging chemistries, new exposure routes (e.g., inhalation), and the unique exposures received by sensitive subpopulations		
2.6.4	Measurement of renal and transporter activity on 150 PFAS to more accurately predict renal excretion and entero-hepatic recirculation to inform extrapolation from laboratory to human doses	Publication
2.6.5	Refined TK models and data to address important exposure routes	Publication
2.6.6	Life-stage and sensitive population characterization and modeling	Publication
2.6.7	New mathematical models to predict HTTK for chemicals with no measurements	Publication
2.6.8	Understanding chemical distribution within in vitro assays	Publication
2.6.9	Reducing the uncertainty in rapid TK models	Publication
2.6.10	Chemical parent-metabolite PBTK modeling and database for read-across	Publication

2.6.11	High throughput toxicokinetic aquatic species model for ecological risk prioritization	Publication
2.6.12	Integration of exposure and tissue dosimetry models with quantitative adverse outcome pathways	Publication
Output 2.7: Develop, evaluate, and apply next-generation monitoring methods, alongside traditional monitoring methods, to identify critical sources and pathways of human and ecological exposures		
2.7.1	A report on the strengths and limitations of non-targeted analysis (NTA) methods for rapid chemical monitoring	Dataset
2.7.2	A model for estimating chemical concentrations in environmental and biological media using non-targeted analysis (NTA) measurements	Dataset
2.7.3	Refinements to high-throughput exposure estimates using non-targeted analysis (NTA) measurements of environmental media and products	Dataset
2.7.4	New human biomonitoring data, measured using non-targeted analysis (NTA) methods, to refine consensus human exposure models	Dataset
2.7.5	A rapid screening technique for identifying metabolites and transformation products via non-targeted analysis (NTA) measurements and in silico predictions	Dataset
2.7.6	Case-study application of non-targeted analysis (NTA) for chemical characterization in a rapid response scenario	Dataset
2.7.7	Targeted measurement data for high priority chemicals to characterize their properties and behaviors in support of risk-based prioritization	Dataset
Output 2.8: Develop methods to characterize composition of and exposure to chemical substances of unknown or variable composition, complex reaction products, and biological materials		
2.8.1	Data tools to detect components/families of Unknown or Variable compositions, Complex reaction products and Biological materials (UVCBs) in non-targeted analysis data	Publication
2.8.2	Exposure applications of data tools to UVCB case studies: Fingerprinting, classification models, and effects directed analysis	Dataset
Research Area 3: Emerging Materials and Technologies (EMT)		
Output 3.1 Evaluate environmental release of ENMs and assess and model human and ecological exposures to ENMs, including data for nanoenabled consumer products		
3.1.1	Analysis of filaments, emissions, and products of 3-D printing processes	Publication
3.1.2	Characterization of human exposure to 3-D printing processes	Publication
3.1.3	Update Risk Assessment Framework for Nanomaterials	Summary Report
3.1.4	Characterization of transport, transformation and fate of nano-enabled pesticides	Publication

3.1.5	Characterization of environmental impacts of nano-enabled pesticides	Publication
3.1.6	Model fate and transport of nanomaterials in surface waters	Publication
3.1.7	Characterization of weathering, release, and transformation of nanomaterials from nano-enabled consumer products	Publication
3.1.8	A critical review of the human and ecological exposure to quantum dots	Publication
Output 3.2 Develop a user interface for ORD's existing nanomaterials database: NaKnowBase		
3.2.1	Development of an improved NaKnowBase	Model
3.2.2	Expanded input/output capabilities for NaKnowBase	Database
3.2.3	Potential adverse activities prediction of novel nanomaterials	Model
3.2.4	Public accessibility for NaKnowBase	Database
Output 3.3 Evaluate the current regulatory approaches for products and processes involving emerging biotechnology (synthetic biology, genome editing, and metabolic engineering) and determine future research needs to support risk assessments		
3.3.1	Convene a workshop on research needs for risk assessments of emerging biotechnology products in regulatory applications and develop an EPA report that summarizes the findings	Report
Research Area 4: Adverse Outcome Pathways (AOP)		
Output 4.1 Coordinate with the scientific community to advance the AOP framework, grow the AOP knowledgebase, and foster broader acceptance and use of AOPs in decision making		
4.1.2	Advancing the AOP framework	Publication
4.1.3	Systematic review and systematic mapping for AOP development and evaluation	Publication
4.1.4	Upgrades to the AOP knowledgebase and AOP database	Model
4.1.5	Growth and development of the AOP knowledgebase	Report
Output 4.2 Develop and conduct strategic in vitro and in vivo studies for high-priority AOPs to help establish validity of NAMs approaches, support predictive model development, and reduce vertebrate animal testing through in vivo testing refinements for decision-relevant endpoints		
4.2.1	Evaluate NAMs for reproductive toxicity testing: Establishing linkages to AOP networks for male and female reproductive health outcomes and testing new and emerging chemicals and mixtures of concern	Publication
4.2.2	Evaluating NAMs for assessing lung toxicity of inhaled methodologically-challenging chemicals	Publication
4.2.3	High throughput screening and environmental risk assessment: state of the science and emerging applications	Publication
4.2.4	Identification of priority neurotoxicology/developmental neurotoxicology AOPs and linkages of key events with HTT DNT screens	Publication
4.2.5	Leveraging organotypic in vitro models and bioinformatic analysis of electronic medical records to develop AOPs describing the effects of inhaled toxicants	Publication

4.2.6	Quantitative AOPs and computational tools for predicting thyroid disruption leading to adverse apical outcomes in amphibian and fish models	Publication
4.2.7	Quantitative AOPs for thyroid disruption and neurodevelopmental outcomes. Improving biomarkers and defining mechanisms	Publication
4.2.8	Quantitative in vivo validation and application of in vitro high-throughput (HT) assays for thyroid hormones disrupting chemicals using physiologically-based models	Publication
Output 4.3 Conduct studies to elucidate and define biological points of departure and susceptibility factors that need to be considered for quantitative application of AOPs		
4.3.1	Case studies to identify epigenetic susceptibility factors for ecological and human health	Publication
4.3.2	Computational modeling approaches and case study validation to identify genetic-based susceptibility factors to environmental chemical exposures	Publication
4.3.3	NAM development to establish early quantifiable indicators of adverse outcomes	Publication
4.3.4	Quantitative AOP development for aromatase inhibition	Publication
4.3.5	Quantitative AOP development for respiratory tract remodeling	Publication
Output 4.4 Develop rationale and case studies that apply AOPs and HTT data to inform test-order decisions and establish scientific support for waiving testing requirements for pesticides as part of the implementation of FIFRA		
4.4.1	Case studies for advancing AOPs and use of transcriptomic points of departure putative pesticide active ingredients for waiving 2 year test requirements	Publication
4.4.2	Identification of genetic and epigenetic biomarkers associated with the neonicotinoid imidacloprid in zebrafish	Publication
4.4.3	A set of gene expression biomarkers and activation levels predictive of rat liver cancer in short-term exposure studies	Publication
Output 4.5 Provide AOP knowledge along with conceptual frameworks and case study demonstrations that support the use of high-throughput or other NAMS data in expedited risk assessments for data poor chemicals		
4.5.2	Ecological risk-based screening approaches for large inventories of data poor chemicals	Publication
4.5.3	Application of new approach methodologies and AOPs in the derivation of ambient water quality criteria or water quality benchmarks	Publication
4.5.4	Application of 21st century bioanalytical tools to identify high-priority chemical constituents of poorly characterized complex mixtures: a case study with UVCBs	Dataset
4.5.5	Evaluating the relative sensitivity of epigenetic effects versus pathway-based or apical effects in setting water quality benchmarks: a case study with ethynylestradiol in fathead minnow	Publication

Output 4.6 Conduct case studies that demonstrate how pathway-based data from existing sources, or from effects-based monitoring and surveillance approaches, can be used along with AOPs to inform risks and associated management actions		
4.6.1	Great Lakes restoration initiative contaminants of emerging concern	Publication
4.6.2	Advancement of AOPs for capturing ecologically-relevant effects of weak estrogen receptor agonists such as PFAS	Publication
4.6.3	Bioactive contaminants of emerging concern: Prioritizing future research based on in-vitro bioassays and predicted chemical-gene interactions	Publication
4.6.4	Development and application of ecosystem level projection models coupled with AOPs	Publication
4.6.5	Application of pathway-based monitoring approaches for evaluation of remedy effectiveness at a Great Lakes clean-up site: Case study in the Erie Pier Ponds, Duluth, MN	Publication
4.6.6	Non-invasive and AOP-linked microRNA biomarker development for toxicological studies and population biosurveillance	Publication
4.6.7	Detecting genetic/epigenetic changes associated with long-term exposure to eight-contaminant mixture found in the Great Lakes watershed	Publication
4.6.8	Metabolomics in regulatory toxicology: Best practice, reporting standards, and quality assurance/quality control	Publication
4.6.9	Combining cell-based metabolomics and lipidomics with cheminformatics tools for untargeted screening and prioritization of vertebrate-active stressors following exposures to complex	Publication
4.6.10	Using an AEP/AOP-based taxonomy of chemical interactions to organize mechanistic data on chemical interactions and to establish mechanistic-based definitions for concepts in mixture toxicology	Publication
4.6.11	Application of 21st century bioanalytical tools to identify sources and effects of bioactive contaminants	Publication
Output 4.7 Develop AOPs relevant to human health and ecological impacts of perfluoroalkyl substances (PFAS) and evaluate applicability across species, chemical groupings, and mixtures		
4.7.1	Development of adverse outcome pathways (AOPs) suitable for assessing the ecological risk of per- and polyfluoroalkyl substance (PFAS)	Publication
4.7.2	In vitro to in vivo translation: targeted in vivo testing to evaluate in vitro and in silico predictions of PFAS toxicity related to thyroid disruption using an amphibian model	Publication
4.7.3	An AOP approach for evaluating adverse effects in vulnerable human populations: PFAS Case Study	Publication
4.7.4	Developmental and reproductive toxicity of in utero and early life exposures to per- and polyfluoroalkyl substances (PFAS) including individual chemicals and mixtures	Publication
4.7.5	Towards an avian AOP for PFAS: Assessment of exposure to and effects of per- and polyfluoroalkyl substances (PFAS) in tree swallows	Publication

4.7.6	PFHxS and developmental neurotoxicity (DNT): Does thyroid hormone action play a role?	Publication
4.7.7	Accelerate development of PFAS-related adverse outcome pathways (AOPs) to provide mode-of-action (MOA) context	Publication
Research Area 5: Virtual Tissue Modeling (VTM)		
Output 5.1 Develop, characterize, and apply organotypic and complex tissue models that bridge between in vitro and organismal assays for decision-relevant endpoints		
5.1.1	Development and application of an in vitro human thyroid organotypic culture model for chemical screening	Publication
5.1.2	Enhanced organotypic fusion model to assess chemical-induced developmental toxicity	Publication
5.1.3	Application of organotypic in vitro tissue models of the respiratory tract to characterize the effects of inhaled chemical exposures	Publication
5.1.4	Directed differentiation of human induced pluripotent stem cells for developmental toxicity screening	Publication
Output 5.2 Integrate and evaluate phenotypic responses in human cell based in vitro and virtual tissue model systems to predict chemical hazard during growth and development		
5.2.1	Developmental toxicity predictive model	Publication
5.2.2	Human pregnancy microphysiological systems models	Publication
5.2.4	Organotypic models of early brain development to evaluate chemical-induced toxicity	Publication
5.2.5	Organotypic model of cellular transformation to evaluate chemical-induced developmental toxicity	Publication
5.2.6	Organotypic model for screening thyroid hormone disruptors	Publication
Output 5.3 Develop and apply in silico agent-based and computational models to evaluate the effects of chemicals on biological pathways critical for lifestage endpoints		
5.3.1	Performance-based computational model for predicting developmental toxicity and its application to human pregnancy	Publication
5.3.2	Systems modeling to predict chemical effects on neurovascular development	Publication
5.3.3	Molecular characterization of toxicological tipping points via transcriptomic signatures of adaptation and adversity	Publication
5.3.4	Computational Intelligence: expanding the 'virtual embryo' portfolio for predictive toxicology	Model
5.3.5	Agent-based model and simulation manifold for developmental computation with data from chemical effects on pluripotent stem cells	Model
5.3.6	Modeling the retinoid system during developmental processes and toxicities	Model
5.3.7	Inhalation dosimetry: Multi-scale systems model framework and selection strategy	Report

Research Area 6: Ecotoxicological Assessment and Monitoring (ETAM)		
Output 6.1 Develop and apply models to translate data from submitted studies into input for models that estimate population- and landscape-level impacts of pesticide use		
6.1.1	Amphibian population models translating developmental effects with ecologically relevant context	Publication
6.1.2	Generalization of the MCnest model to estimate a wider range of avian risks	Model
6.1.3	Fish toxicity translator model and computational workflow development	Model
6.1.4	Development of methods to extrapolate results of standard toxicity tests to protect natural populations experiencing pulsed and fluctuating exposures to environmental contaminants	Publication
6.1.5	Extrapolation of the results of fish chronic toxicity tests to protect wild populations from long-term exposures	Publication
6.1.6	Species Sensitivity Distributions (SSD) Toolbox	Model
6.1.7	Development of a flexible R environment for toxicity translation for aquatic invertebrates	Model
Output 6.2 Develop methods and data to assess the impacts of pesticides on honey bee (Apis mellifera) and non-Apis bees, apply species extrapolation techniques to determine sensitivity differences across species, and further develop and apply honeybee colony simulation models to support pesticide assessments		
6.2.1	Honeybee colony models that incorporate pesticide exposures and effects	Publication
6.2.2	MCnest hummingbird module and application	Model
6.2.3	Targeted and non-targeted analysis of pesticides and other contaminants in honey bee hive matrices	Publication
6.2.4	Effects of pesticide exposure on bumble bee health, immunocompetence and drone fitness	Publication
6.2.5	Defining the taxonomic domain of applicability for nicotinic acetylcholine receptor activation and ecdysone receptor activation adverse outcome pathway networks	Publication
Output 6.3 Improve efficiency, enhance analytical capabilities, and periodically update content of the ECOTOX Knowledgebase, in general and for specific chemicals of interest		
6.3.1	ECOTOX Knowledgebase quarterly updates, including data on new chemicals and updated software and user interface functionality	Database
6.3.2	Annual updates to ECOTOX Knowledgebase User Guide and Standard Operating Procedures	Publication
6.3.3	Communication and training for ECOTOX Knowledgebase	Technical Fact Sheet
6.3.4	Improved efficiency and documentation in the literature search and data curation processes for the ECOTOX Knowledgebase	Dataset
6.3.5	Increased interoperability and methods to incorporate ECOTOX data with other tools/databases	Publication
6.3.6	PFAS-specific literature searches, identification and data extraction of ecotoxicological data for use in Agency risk assessments	Dataset

Output 6.4 Advance approaches for using surrogate species in ecological risk assessment, including assessment of uncertainty of cross-species extrapolations in minimal data scenarios, evaluation of species-response to high-priority pesticides, and extrapolation from mammalian to fish metabolism pathways		
6.4.1	Demonstrated Interoperability Between SeqAPASS and the ECOTOX Knowledgebase to inform challenges in cross species extrapolation relative to high-priority pesticides	Publication
6.4.2	Coupling in silico approaches with chemical proteomics to inform relative bioaccumulation potential of per- and polyfluorinated alkyl substances across species	Publication
6.4.3	Characterization of multi-omics responses of aquatic species over time and concentration to high priority chemicals including pesticides	Publication
6.4.4	Ecological effects-based QSARs for pesticide modes-of-action	Report
6.4.5	Development of ecosystem level projection models coupled with adverse outcome pathways and results from the Sequence Alignment to Predict Across-Species Susceptibility tool for fish and bees	Model
6.4.6	Comparison of PFAS metabolic pathways across species	Publication
6.4.7	Molecular and functional characterization of receptor targets in aquatic species and the development of cross-species screening assays for species differences in sensitivity and/or selectivity	Publication
6.4.8	Pesticide uptake, bioaccumulation, biomarker discovery and biological response in terrestrial amphibians	Publication
Output 6.5 Develop improved approaches to protect threatened and endangered species from exposures of chemicals released to the environment		
6.5.1	Development of watershed and fine scale modeling to estimate pesticide exposure concentration	Report
6.5.2	Spatially-explicit approaches to probabilistically evaluate chemical mixtures and/or cumulative exposures in Ecological Risk Assessment of listed species in a vernal pool case study	Report
6.5.3	Approaches to use minimal toxicity effects data for probabilistic assessments	Publication
6.5.4	Bayesian model selection for amphibian exposure	Publication
Output 6.6 Improve ecological methods and models for predicting exposure, accumulation and effects of PFAS and other methodologically challenging compounds		
6.6.1	Methodically Challenging Chemicals (MCCs): Bioaccumulation of MCCs by fish and benthic invertebrates	Publication
6.6.2	Use of in vitro-in vivo extrapolation (IVIVE) to predict biotransformation of methodologically challenging compounds in fish	Publication
6.6.3	Ecological outcomes of exposure to high priority PFAS compounds, mixtures and contaminated sites	Publication
6.6.4	Bioaccumulation of PFAS compounds in aquatic organisms	Assessment Document

Research Area 7: Chemical Safety Analytics (CSA)		
Output 7.1 Continued expansion of content and refinement of processes associated with curation and quality assurance documentation for databases and lists of chemical substances, structures and samples		
7.1.1	DSSTox chemical & list curation	Dataset
7.1.2	Expanding DSSTox capabilities for handling complex substances and distributed databases	Dataset
7.1.3	Management and expansion of chemical screening libraries supporting ORD testing programs	Dataset
7.1.4	Chemical screening library analytical data management and review	Database
7.1.5	Accurate chemical curation, registration, and mapping tools	Dataset
7.1.6	Expanded PFAS chemical library and analytical QC information for program offices, regions, states and other stakeholders	Database
Output 7.2 Develop data, tools, and models to inform the taxonomic relevance of AOPs and to support cross-species extrapolation for human health and ecological assessments		
7.2.1	Maintenance and public release of enhanced versions of the Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) Tool	Model
7.2.2	Developing advanced molecular modeling methods to inform predictions of chemical susceptibility to enhance the Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) Tool	Publication
7.2.3	Defining how broadly high-throughput screening assay results May be extrapolated across species by understanding conservation of endocrine pathways	Report
7.2.4	Web-ICE Database update	Model
Output 7.3 Expand modeling capabilities to predict potential metabolites and environmental transformation products for priority chemicals, including emerging contaminants		
7.3.1	Updated Chemical Transformation Simulator with expanded prediction capabilities for metabolic and environmental transformations based on curated database of reported transformation pathways and rates	Model
7.3.2	Enhancement of the Chemical Transformation Simulator through development and implementation of improved models for prediction of transformation rates and likelihood of transformation product formation	Model
7.3.3	Laboratory/field-sample studies and model refinement to improve predictions of environmental transformations and partitioning of PFAS	Publication
Output 7.4 Develop new and improve existing structure activity relationship models to support risk assessment for industrial chemicals, pesticides, and emerging contaminants		
7.4.1	Research and development of modeling best practices	Publication
7.4.2	Development of dataset and QSAR models to support exposure estimation	Dataset
7.4.3	Development of datasets and QSAR models to support hazard estimation	Model

Output 7.5 Further develop and apply chemotype enrichment approaches and categorization/classification schemes to support local chemical domain modeling and read-across workflows for aiding the interpretation and prediction of bioassay/toxicity outcomes		
7.5.1	Establish consistent chemical structure-based categories to replace subjective category naming	Database
7.5.2	Further develop and apply chemotype-enrichment workflow (CTEW) approaches to generate structure-activity hypotheses in local chemistry domains in support of read-across and HTT assay analysis	Publication
7.5.3	Application of the chemotype-enrichment workflow to derive global insights from high-throughput screening data such as ToxCast	Publication
7.5.4	Enhancing the Generalized read-across (GenRA) approach to address other similarity contexts beyond structural similarity	Model
7.5.5	Read-Across and categorization to understand the PFAS screening results	Publication
7.5.6	Evaluating the relevance of existing non-cancer oral Thresholds for Toxicological Concern (TTC) values and developing new TTCs for environmental chemicals	Model
7.5.7	Approaches for aligning chemical inventories with AOPs / AOP-based chemical grouping	Publication
7.5.8	Enhance capabilities of chemical categorization and read-across tool (GenRA) to evaluated PFAS	Publication
Research Area 8: Integration, Synthesis, and Informatics (ISI)		
Output 8.1 Develop unified and extensible software infrastructure to support all ISI data streams and applications, integrating legacy and new applications, data streams and models		
8.1.1	Migration of legacy dashboards to CompTox Chemicals Dashboard	Database
8.1.2	Improve CompTox Chemicals Dashboard user experience	Database
8.1.3	Software support for mass spectrometry: Suspect, targeted and non-targeted analysis	Database
8.1.4	Extend CompTox Chemicals Dashboard to support new types of data and visualization	Database
8.1.5	Develop RapidTox Workflow Environment	Model
8.1.6	Deliver access to real-time model predictions	Model
8.1.7	PFAS NAM Dashboard	Database
Output 8.2 Develop and deliver rapid assessment workflows and applications for chemical evaluation across a range of hazard and/or risk-based decision-contexts using multiple data streams, models and visualizations		
8.2.1	Deliver use-case workflows to support RapidTox	Model
8.2.3	Development and application of a "Site-specific Chemical Prioritization" workflow	Model
8.2.4	Development and application of a "Site-specific Assessment" workflow	Model

8.2.5	Development and application of a "Mixtures Screening and Assessment" workflow	Model
Output 8.3 Develop informatics to support rapid and seamless use of hazard, exposure, NAM and other data streams in decision making, as applications advance beyond prioritization into higher tier assessments		
8.3.1	Deliver a centralized document registering system – Clowder	Model
8.3.2	Develop and Implement a computational framework to support CSS	Dataset
8.3.3	Development of Chemical-Biological Data Hub for context based data integration	Dataset
8.3.4	Infrastructure support for data set delivery to the public	Dataset
Output 8.4 Continued development and curation of databases to support chemical safety decision making, including mammalian toxicity, exposure, and NAM data		
8.4.1	In vivo data for risk assessment tools and modeling	Database
8.4.2	In vitro data for hazard prediction and screening workflow tools	Database
8.4.3	Transcriptomic and phenotypic profiling in vitro data for Tier 1 chemical safety evaluation	Database
8.4.4	Chemistry and physicochemical property data as the foundation for research and risk	Database
8.4.5	Toxicokinetic and high-throughput toxicokinetic data as tools for translation of doses	Database
8.4.6	Exposure and exposure pathway data for risk assessment tools and modeling	Database
8.4.8	Model and dataset registration to enable accessibility and interoperability of information	Database
8.4.9	Extract physicochemical property, environmental fate, and bioaccumulation data from public sources	Dataset
8.4.10	Generate experimental physical/chemical property measurements on select PFAS to fill data gaps	Dataset
8.4.11	QSAR Models for physical/chemical properties, environmental fate, and bioaccumulation	Publication
Output 8.5 Develop, validate, and integrate models to fill data gaps and integrate NAM data to support chemical safety decision making		
8.5.1	Tiered testing model for thyroid disruption to predict thyroid-related MOA and thyroid-related Points of Departure	Model
8.5.2	NAM-based models to predict chemical Mode of Action	Model
Output 8.6 Develop risk-based approaches and computational tools to prioritize chemicals for program specific applications, integrating existing and new data on, for example, chemical properties, hazard, exposure, persistence, and bioaccumulation		
8.6.1	Workflow to support TSCA prioritization	Model
8.6.2	Risk-based toxicological testing and assessment strategy for PFAS	Report