CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
High Throughput Toxicology	Develop and Implement Deiodinase Activity Assay for Screening EDSP Chemicals	Deiodinase enzymes perform critical roles in vertebrate thyroid hormone homeostasis by maintaining the balance between having sufficient active thyroid hormone when and where it is needed, and the catabolism of hormone when signaling needs to be reduced. Development of a 96-well plate assay to assess chemical inhibition of deiodinase activity in vitro and demonstration of its application to screening large chemical libraries will be reported in this product. This supports the EDSP's need for higher-throughput screening assays to address additional molecular initiating events with the potential to disrupt normal thyroid hormone signaling.	journal article	Mike Hornung	NHEERL
High Throughput Toxicology	Synthesis of screening data for ToxCast Ph1_v2 chemicals to detect thyroid NIS iodide uptake inhibitors	This is a synthesis of data from a screening approach that identifies chemicals in the ToxCast Phase 1_v2 library that inhibit the sodium/iodide symporter (NIS)-mediated uptake of iodide by the thyroid. Chemicals will be screened using an iodide uptake assay, which utilizes a stable human NIS-expressing cell line, along with a complementary cell viability assay. Results from both assays will be incorporated to provide a tool for ranking potential NIS inhibitors that can be used to initially prioritize chemicals or classes of chemicals for further investigation. This work is in support of the Agency's EDSP21 efforts to identify thyroid disrupting chemicals.	journal article	Susan Laws, Tammy Stoker	NHEERL
High Throughput Toxicology	Mathematical model(s) for chemical priority setting that integrate data from multiple alternative assays for DNT	Mathematical (machine learning) models will be developed to combine chemical potency data from multiple alternative assays (e.g. zebrafish development in vivo, neural cell development in vitro) to rank compounds based on level of concern for developmental neurotoxicity. The results can be used for prioritizing additional testing for potential developmental neurotoxicants.	journal article	Tim Shafer	NHEERL
High Throughput Toxicology	Role of microbiota in the normal development of zebrafish	This work characterizes the effect of microbiota on locomotor activity in zebrafish. The assay developed and characterized here will ultimately be used to test whether microbiota modify the developmental toxicity of environmental chemicals.	journal article	Tamara Tal	NHEERL
High Throughput Toxicology	Develop predictive computational models of systemic toxicity	High-throughput toxicity testing generates data on thousands of chemicals in hundreds of assays. Data from single high-throughput assays can be difficult to apply in risk assessment. Instead of focusing on single assays, models of in vitro bioactivity profiles (i.e., "signatures") are developed for improved interpretation the significance of the in vitro testing data. This work will use statistical and biological models to generate predictive signatures consistent with the likelihood of a chemical to cause systemic toxicity in vivo and probability estimates for the predictions.	journal article	Matt Martin	NCCT

CSS - FY17 Deliverables (UPDATED 10/27/16)					
Project	**Product Title**	**Product Description**	**Product Type**	**Product Lead**	**L/C**
High Throughput Toxicology	**Generate high-throughput transcriptomic data to evaluate potential toxicological effects and modes of-action**	Current ToxCast assays cover a limited biological space for toxicity. This work will assess and adapt high-throughput transcriptomic technologies in order to cover a broader biological space, without greatly increasing cost. Analysis of the transcript profiles will allow the identification of chemicals that appear to be selective for a biological target and the associated putative mode-of-action, or the derivation of transcriptional points of departure based on biological activity for chemicals showing non-selective activity. The transcriptomics data could be used as a first screening step, followed by more targeted testing in molecular and cellular assays. The goal for FY17 is a gene expression analysis platform that can be used as a screening tool in multiple cell types.	**database**	**Matt Martin**	**NCCT**
High Throughput Toxicology	**Develop methods incorporating xenobiotic metabolism into in vitro high-throughput screening assays to increase in vivo relevance and identify potential bioactivated chemicals**	A challenge of high-throughput toxicology screens is the limited metabolic capacity of the available molecular and cellular assays. The lack of metabolism in these systems could lead to false negatives, as well as reduce confidence in the biological relevance of chemical perturbations in these assays. This work will develop methods that include metabolic capacity in existing high-throughput assays.	**journal article**	**Steve Simmons, Brian Chorley**	**NCCT, NHEERL**
High Throughput Toxicology	**Develop higher throughput approaches for screening volatile chemicals to prioritize chemicals as potential inhalation toxicants**	Current high-throughput testing systems have limited ability to screen volatile compounds. These compounds are difficult to administer to cellular and molecular assays performed in liquid media This journal article will provide a proof of concept for a lower throughput screening assays of volatiles, as well as describe the challenges for increasing throughput.	**journal article**	**Mark Higuchi**	**NHEERL**
Rapid Exposure & Dosimetry	**Database of chemical use and consumer product composition information to support new TSCA exposure assessment requirements**	The current understanding of the total numbers of chemicals to which humans are exposed is limited. New, high-throughput exposure prediction models have recently been developed for rapid chemical screening. These computational models require use and chemical composition data for consumer products, which is unavailable for large numbers of products. This work will generate measured composition data from a range of consumer products (including recycled products) to parameterize Agency exposure models and other decision support tools.	**journal article**	**John Wambaugh**	**NCCT**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Rapid Exposure & Dosimetry	**Higher throughput analytical chemistry methods, data processing workflows, and resulting exposure data (e.g., for articles, environmental media, biological media) to support rapid exposure assessment and risk-based decisions**	High-resolution mass spectrometry (MS) has been used to detect thousands of unknown features, identified by accurate mass and retention time, in environmental media, biological media, and articles. These detections, however, are not readily identifiable as chemical structures. This product will therefore focus on higher-throughput workflows for translating unknown MS features into "tentative", "probable", and "confirmed" chemical structures. Such workflows by necessity include: generation and cleaning of raw MS data, archival of feature information in standardized databases, querying of MS libraries and other databases for candidate chemical structures, and interpretation of candidate structures using innovative modeling tools. The product will include: 1) manuscripts detailing the higher-throughput workflows and their application towards the analysis of environmental and/or biological samples; 2) computational tools for implementing components of the workflows (available via the USEPA CompTox Dashboard); and 3) exposure data (i.e., structures detected in media) generated from utilization of the workflows. It is expected that the workflows, tools, and data will be used by the exposure science community for advancing application of non-targeted analyses, and by ORD/CSS scientists for chemical prioritization and model evaluation.	**journal article**	**Jon Sobus**	**NERL**
Rapid Exposure & Dosimetry	**Development of pharmacokinetic models predicting internal doses for hundreds of chemicals and facilitating exposure based risk prioritization of chemicals**	Use of bioactivity data from high-throughput assays for risk decisions is hampered by uncertainties in estimating exposure dose. This product will generate the data and tools necessary to more directly compare bioactive concentrations identified by ToxCast bioassays to Rapid Exposure forecasts. Specifically, this product will refine previous methods to extrapolate from in vitro data to human exposures, with a focus on replacing the constant infusion exposure route that is currently used with more realistic human exposure pathways.	**journal article**	**John Wambaugh**	**NCCT**
Rapid Exposure & Dosimetry	**An in vivo PK data set for statistical analysis of High Throughput ToxicologyK model assumptions (Contributing Product)**	The results from in vivo pharmacokinetic data collected on 26 ToxCast chemicals will be compared to predictions from in vitro high through put PK (HTPK) models. The objective of this study is to assess the ability of current in vitro HTPK models to predict accurately in vivo PK parameters important for describing the relationship between chemical exposure and adverse outcome.	**journal article**	**Jane-Ellen Simmons**	**NHEERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Rapid Exposure & Dosimetry	**Evaluation of ExpoCast methods for biomarker-based exposure inference and forward human exposure prediction using a case-study dataset of paired biomarker and media concentration measurements**	Near-field (e.g., consumer product) use of chemicals has been shown to be a critical predictor of exposures inferred from biomarker measurements from the National Health and Nutrition Examination Survey (NHANES). Under the ExpoCast program, ORD has been refining high-throughput methods for 1) developing exposure inferences for left-censored biomarker measurements (i.e. those with many measurements below the limit of detection), and 2) predicting forward near-field exposures using mechanistic models such as the high-throughput Stochastic Human and Dose Simulation (SHEDS-HT) model. Here, these refined inference and prediction methods are evaluated using a dataset of matched residential media (air and dust) and biomarker concentrations from a population of 120 women living in Cape Cod, Massachusetts. The product will describe new mathematical methods for handling left-censored datasets (thereby increasing the number of chemicals for which data available for model evaluation) and demonstrate the value added of considering direct and indirect near-field consumer product pathway exposures in interpreting media-specific exposure measurements. These methods provide confidence in the predictive ability of forward ExpoCast exposure model. Estimates from these models are being incorporated into a structured statistical framework for development of consensus predictions for use in risk-based prioritization and screening of chemicals for further study under the CSS program.	**journal article**	**Kristin Isaacs**	**NERL**
Rapid Exposure & Dosimetry	**Statistical Modeling to Characterize Chemicals Identified in Non-targeted/Suspect Screening Analysis of Consumer Products**	New measurement data are being generated under the ExpoCast to identify and quantify chemicals in consumer formulations and articles (including recycled materials) in support of high-throughput chemical prioritization. This product will include analysis of tentatively-identified or confirmed compounds with existing structure-based tools, chemical use databases, or chemical classification ontologies to characterize their uses (e.g. functional use, sector of use), chemical classes, or sources (e.g. intentional addition, degradation, or contamination). These analyses will elucidate potential exposure pathways for thousands of chemicals in the near-field environment and inform high-throughput prediction of exposures in ExpoCast.	**journal article**	**Katherine Phillips**	**NERL**
Rapid Exposure & Dosimetry	**Evaluting predictive ability of high-throughput ecological exposure models through comparisons with sampling data from a variety of media**	The first-generation of high-throughput predictions of ecological exposures will be evaluated by integrating sampling data collected by the USGS and USEPA. Statistical methods will be developed to adjust the sparse matrix of ecological samples to be more nationally representative. The paper will describe the methods, and provide R code with documentation, for making more accurate ecological exposure predictions.	**journal article**	**Woody Setzer**	**NCCT**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Rapid Exposure & Dosimetry	**Measuring and Modeling Surface Sorption Dynamics of Organophosphate Flame Retardants in Chambers**	The focus of the Rapid Exposure and Dosimetry project area is to develop the data, tools, and evaluation approaches required to generate rapid and scientifically-defensible exposure and estimates for the full universe of existing and proposed commercial chemicals. Understanding the transport mechanisms of organophosphorus flame retardants (OPFRs) between sources, air, airborne particles, house dust, and interior surfaces in the indoor environment is essential to accurately estimate indoor exposures and develop strategies that enlighten risk assessments and policy decisions to minimize exposures and protect human health. In the research, a time-dependent sorption model has been developed. It integrates monolayer and multilayer sorption mechanisms to characterize the adsorption/desorption dynamics of OPFRs on stainless steel surface through a series of empty chamber studies. The model includes both Langmuir and Freundlich sorption kinetics as well as a characteristic time that describes the transition of sorption from homogeneous to heterogeneous. The chamber tests involve two types of stainless steel chambers (53-L small chambers and 44-mL micro-chambers) using tris(2-Chloroethyl) phosphate (TCEP) and tris(1-Chlor-2-propyl) phosphate (TCPP) as target compounds. Test results show that the time-dependent sorption model can better represent the adsorption/desorption process in the empty small chamber. The developed model has been applied to predict the gas phase concentrations of OPFRs in the empty micro chamber and the small chamber with an emission source. Comparisons between model predictions and measurement results show the reliability and application of the proposed sorption model. When an SVOC source is tested for emissions in an environmental chamber, interior walls of the chamber may adsorb substantial SVOCs from the air inside the chamber. Sorption by the walls of the chamber will cause underestimation of the emission rate and can be an error source for emissions testing. Poor understanding of SVOC adsorption by impermeable surfaces, such as stainless steel plates, has hindered the interpretation of chamber data for characterizing SVOC sources and sinks. These research results are necessary to interpret the emission and sorption data and improve the source and sink models. The research results will reduce the uncertainties in the input parameters of SVOC models and substantially improve	**journal article**	**Xiaoyu Liu**	**NRMRL**
Adverse Outcome Pathways Discovery & Development	**A portfolio of case studies that highlight novel strategies for developing adverse outcome pathways for cancer, liver disease, and other health outcomes based on early key events**	Adverse outcome pathway descriptions support the development of higher-throughput data streams and alternative assays for chemical screening, prioritization, and tiered testing applications. This product enhances the AOP knowledgebase, provides AOP-based tools and biomarkers for more rapid chemical evaluation, and adds to our understanding of complex AOP networks. Representative cases studies include predictive models, signatures, and assays aligned with early key events in AOPs. This information directly informs efforts to link target pathways of environmental chemicals with adverse outcomes of regulatory relevance.	**journal article**	**Charles Wood, Brian Chorley**	**NHEERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Adverse Outcome Pathways Discovery & Development	**Global analysis of ToxCast targets by SeqAPASS**	Most of the toxicological targets represented in the ToxCast data are of mammalian origin (typically human). Thus, using ToxCast data for ecological applications requires some form of species extrapolation to understand the taxonomic relevance of assay results. One approach is to use the publically available SeqAPASS (Sequence Alignment to Predicts Across Species Susceptibility) tool to evaluate cross species protein sequence similarity. This analysis will assess the conservation of ToxCast-relevant protein targets across taxa to provide insights on how these data may be applied in an ecological context.	**journal article**	**Carlie LaLone**	**NHEERL**
Adverse Outcome Pathways Discovery & Development	**Integration of chemical-specific exposure and pharmacokinetic information with chemical-agnostic AOP framework to support high throughput risk assessment**	High-throughput *in vitro* assays screen for hazards through identification of perturbations on technological targets, and the AOP framework can be used to provide a biological context for these screening results and link them to adverse outcomes relevant to human and ecosystem health. For risk assessment, *in vitro* hazard data interpretable by AOPs need to be connected to chemical-specific exposure and pharmacokinetic information, which can be accomplished in a tiered manner. This product will include multiple case studies, in the format of peer-reviewed publications and presentations, as well as associated databases to improve understanding of the information and appropriate approaches required to predict exposure and pharmacokinetic information when data are limited.	**journal article**	**Cecilia Tan**	**NERL**
Adverse Outcome Pathways Discovery & Development	**Case studies using the AOP framework and pathway-based data to evaluate and develop in vivo, in vitro, and non-lethal approaches for assessing adverse effects on biota residing in impacted Great Lakes ecosystems and Western rivers**	High throughput in vitro, in vivo, and non-lethal approaches that provide a rapid and sensitive assessment of exposure to environmental contamination are needed to improve risk assessments. However, clear connections between these early indicators and the adverse outcomes upon which regulations are based (e.g., reproduction, survival, etc.) are required to solidify their utility. This product features a series of case studies designed to develop and refine these linkages through the use of adverse outcome pathways at sites of high importance to our Regional and Program Office partners.	**journal article**	**Drew Ekman**	**NERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)					
Project	**Product Title**	**Product Description**	**Product Type**	**Product Lead**	**L/C**
Adverse Outcome Pathways Discovery & Development	**Establishing level of concern for chemical-induced enhanced thyroid hormone metabolism in amphibians using "middle-out" investigation of a putative AOP**	A number of chemicals can induce hepatic metabolizing which may enhance the clearance of thyroid hormones in vertebrates. While receptors mediating such induction are well characterized in mammals, the specific target(s) chemicals may interact with to cause such effects in amphibians are unknown. A "middle-out" approach to AOP development and testing will be employed to determine the relevance of this putative AOP for amphibians and to elucidate, if possible, the relevant molecular initiating event(s). A number of classic mammalian inducers of enhanced thyroid hormone clearance were tested in vivo using various study designs in the Xenopus model to evaluate whether an adverse thyroid effect could be demonstrated. Additionally, biomarkers of liver enzyme induction evaluated and compared to other diagnostic indicators of thyroid axis disruption. This is an example of the utility of the AOP framework to characterize taxonomic applicability of AOPs.	**journal article**	**Sigmund Degitz**	**NHEERL**
Adverse Outcome Pathways Discovery & Development	**Adverse outcome pathway linking disruption of fetal androgen signaling to phenotypic impacts on sexual differentiation and implications for extrapolating in vitro assessments of chemical-AR interactions to in vivo outcomes**	Identifying MIEs and key events for different AOPS in the Androgen Signaling Pathway is critical to determining if they provide accurate, quantitative predictions of the adverse postnatal effects of in utero exposure to EDCs and other chemical and non-chemical stressors that disrupt male sexual differentiation in utero. This helps to address the question of "What is the biological relevance of the in vitro and/or in utero fetal alterations?"	**journal article**	**Earl Gray**	**NHEERL**
Adverse Outcome Pathways Discovery & Development	**Conceptual framework for the application of AOPs and pathway-based data for rapid development of ambient water quality criteria for aquatic life**	The Office of Water has expressed interest in developing rapid approaches for water quality criteria development. It is envisioned that a number of CSS tools and data can be brought together in a systematic and integrated fashion to address that need. This product will outline an initial conceptual framework that will be tested and revised in subsequent years through application to specific criterion development case studies.	**journal article**	**Dan Villeneuve**	**NHEERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Adverse Outcome Pathways Discovery & Development	**AOP-Wiki 2.0 release**	The AOP-Wiki has been developed by the EPA as a part of an international collaboration to build an AOP knowledgebase (AOP-KB) to serve as a central repository for global efforts to develop and disseminate AOPs. Following the initial release of the AOP-Wiki in 2013, with a public release in 2014, it has served as the AOP-KB sole module from 2013-2016. In 2016, the AOP-Wiki will have a major new release to coincide with the initial production releases of two additional AOP-KB modules. The OECD Extended Advisory Group for Molecular Screening and Toxicogenomics has stated that the AOP-Wiki will remain the primary module to support the OECD AOP Development Programme for the foreseeable future. At the inception of the CSS AOP DD project, it was decided that the AOP-KB would be the primary mechanism for organizing and delivering the AOP information developed within the project. It currently houses 6 OECD endorsed AOPs (1 from the CSS AOP DD project), 13 AOPs undergoing formal OECD review (3 from the CSS AOP DD project), and over 100 putative AOPs (over half from the CSS AOP DD project) either under development or up for adoption by the academic community. By encouraging AOP development worldwide and capturing the information in an organized fashion, we are able to provide many more AOPs for ToxCast assay interpretation and for identification of new biological targets for future assay development than could possibly be done with the limited intramural resources.	**database**	**Steve Edwards**	**NHEERL**
Virtual Tissues Modeling	**Virtual Developmental Toxicty Laboratory: Access to integrated computational models of embryonic development and human angiogenesis**	Cellular Agent-based models (ABMs) use existing knowledge and empirical data to build computer simulations of complex biological process. ABMs are well-suited to model biological development and can serve as predictive models of developmental toxicity. This product provides a web-based system (i.e., a Virtual Laboratory System) that will enable users to access ABM simulations for specific morphogenetic processes.	**software**	**Tom Knudsen**	**NCCT**
Virtual Tissues Modeling	**Characterization of in vitro fusion experimental model. Use case studies (with several reference chemicals) to evaluate model response**	Virtual Tissue Models are uniquely positioned to capture the connectivity between different scales of biological organization. The focus of the Morphogenetic Fusion Task is to develop a complex 3-D culture model to mimic embryonic fusion events required during development. Morphogenetic fusion is a complex process having contributions from multiple cell types and cell behaviors and is sensitive to chemical disruption. The spheroid model is being developed to evaluate responses to chemicals and perturbation in molecular initiating events or key events involved in fusion-related phenotypes (birth defects). The FY17 product reports outcomes of experiments to evaluate of the spheroid model's responsiveness to model chemicals and to selective disruptors of key events and signaling pathways in palatal fusion.	**journal article**	**Barbara Abbott**	**NHEERL**
Virtual Tissues Modeling	**Culture model for lineage progenitor assay of endocardial morphogenesis**	We will establish an in vitro model of human endothelial cell transition to mesenchymal cells. Current models use mouse or chick ex vivo (explanted) cells to model early development. Using a human based model allows for a direct assessment of chemical effects on a critical step in human heart development	**model**	**Sid Hunter**	**NHEERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Virtual Tissues Modeling	Engagement for enhanced collaboration and amplified impact for CSS and Predictive Toxicology efforts	A meeting between EPA scientists and NCER STAR grantees in the Organotypic Culture Models for Predictive Toxicology Centers (OCM-PT) will be held in FY17 (Saturday March 11 at the 2017 Society of Toxicology annual meeting). There will be themed sessions around cutting edge research projects addressing Agency challenges in identifying and assessing chemicals for developmental toxicity. Presentations by young investigators (e.g., students/postdocs) and an open poster session will be held for OCM-PT research topics invited from the SOT community at large, including EPA scientists. This interdisciplinary co-operative research provides an important focus on 'human organ-on-a-chip' technologies that integrates with 'virtual tissue models' (VTMs) for computational toxicology on AOPs relevant to EPA's public and environmental health protection mission.	other	Barbara Klieforth / Tom Knudsen	NCER / NCCT
Virtual Tissues Modeling	Evaluating microphysiological systems to integrate and improve computational predictive models of neurovascular disruption during development	A current drawback to existing in vitro test methods in ToxCast is the reliance on isolated fragments of complex biological systems. Microphyisological systems are synthetic platforms built from human cells that more accurately mimic complex tissue architecture and functions. Using thyrotrophic neurodevelopment as a case study, this product will review the application of microphysiological systems. This product will establish best practices for more accurate evaluation of in silico models of thyroid hormone kinetics critical for predicting dose-response relationships during development	journal article	Tom Knudsen	NCCT
Virtual Tissues Modeling	Generate TH system knockout model toolkit in zebrafish	We will systematically knockout genes involved in thyroid hormone synthesis using CRISPR-Cas9 targeted mutagenesis in zebrafish. As an initial proof-of-principle, we will generate TPO, dio1, and dio2 F0 mutants.	method	Tamara Tal	NHEERL
Virtual Tissues Modeling	Predictive model of the "tipping point" between adaptive and adverse outcomes using high content imaging data from rat liver cells	A challenge in predicting effects environmental chemical exposure from in vitro assays is the lack of differentiation of adaptive (i.e., homeostatic) and adverse outcomes. This research will develop a data driven model for predict in vitro 'tipping points' between adaptive and adverse cellular states. Use of tipping-point dose, rather than a standard statically based points-of-departure will increase confidence in the use of ToxCast data in risk decisions.	model	Imran Shah	NCCT
Sustainable Chemistry	Manuscript describing the improved cheminformatics platform DSSTox	This journal article will describe the features of the DSSTox 2.0 dashboard that integrate chemical, high through testing data, and exposure predictions.	journal article	Tony Williams	NCCT
Sustainable Chemistry	Manuscript that reports on the development of improved hazard screening models for toxic chemical risk assessment	This research will use conventional and three dimensional QSAR approaches to develop improved predictive models. These models will have a larger applicability domain, and can be used in defining the chemical space of specific AOPs. They will allow in silico screening of a broader range of chemicals than currently available models.	journal article	Mace Barron	NHEERL

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Sustainable Chemistry	**Demonstration of the consensus approach for the calculation of inherent chemical properties required for exposure and effects assessments**	This product will consist of 1) software documentation describing the Physicochemical Properties Calculator (PPC) module of the Chemical Transformation Simulator (CTS) and 2) a journal article comparing the performance of the calculators implemented in the PPC module for a case study. The PPC module is based on a consensus approach for the estimation of physicochemical property values. This module allows the user to compare output generated by a number of calculators that utilize different approaches to predict the same properties. The calculators implemented in CTS include: (1) SPARC (SPARC Performs Automated Reasoning in Chemistry), which uses a mechanistic-based approach, (2) EPI Suite, which uses a fragment-based approach, (3) T.E.S.T. (Toxicity Estimation Software Tool), which uses QSAR-based approaches, and the ChemAxon plug-in calculators, which use an atom-based fragment approach. The output from the PPC module also provides the user with measured data from the PHYSPROP database to facilitate comparison of calculated property values to available measured values.	**journal article**	**Caroline Stevens**	**NERL**
Sustainable Chemistry	**Web-enabled version of T.E.S.T. (Toxicity Estimation Software Tool)**	In 2008, EPA released T.E.S.T. (Toxicity Estimation Software Tool) as a downloadable Java-based application. A web-enabled version of T.E.S.T. is being developed to allow users to estimate toxicity values and physical properties directly from their web browser. This tool will be incorporated within NCCT's iCSS dashboard. The web-enabled version of T.E.S.T. will be an integral part of the alternatives assessment dashboard since it can be utilized to complete hazard profiles for chemical alternatives (in terms of human health hazard, ecotoxicity, and fate scores). Through web-services, the web-based version will allow other EPA tools such as CTS (Chemical Transformation Simulator) to obtain estimates of physical properties and toxicity values.	**software**	**Todd Martin**	**NRMRL**
Emerging Materials	**Nanomaterials relational database populated with extant ORD data**	The nanomaterials relational database will be populated with approximately 80 ORD nanomaterials datasets. This systematic collation of ORD data will be the basis for queries and modeling of the potential relationships between nanomaterial physical and chemical properties and environmental fate, transport, exposure, and hazard.	**database**	**Will Boyes**	**NHEERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Emerging Materials	**Characterization of the Release of Nanoscale Copper Carbonate and Cerium Oxide Employed in Commercial Wood Preservatives and Identification of their Environmental, Health, and Safety Risks in Decision-Support to Research-Needs Framework**	Current wood treatment and surface applications employing nanoscale CeO2 (UV protection) and Cu2CO3(OH)2 (antimicrobial) reflect uses with very high exposure potential and provide a unique opportunity to integrate ORD's scientific "niche" in the areas of exposure, health and ecological effects, and modeling. This novel product-application-based research will examine nanoscale CeO2, Cu2CO3(OH)2 formulations and their transformed products employed in wood treatment\coating by determining their release, exposure, fate, and transformation as well as their health and ecological effects. Research will critically inform the engineered nanomaterial (ENM) decision tree product and provide information to develop integrated adverse exposure pathways (AEPs) to adverse outcome pathways (AOPs) associated with current wood treatment and surface applications employing ENM CeO2 and Cu2CO3(OH)2 commercial products. Unique aspects of this research include the use of commercial nanoscale products, characterization ENM release and transformation associated with a high exposure application, and assessing the effects associated with exposure to mixtures of CeO2, Cu2CO3(OH)2 ENMs and their transformed products. Research findings will inform: i) regulatory uncertainties associated with exposure and effect risks associated with ENM employed in antimicrobial and surface applications with high exposure potential; and ii) newly initiated European Commission LIFE project NanoMONITOR effort that will inform ENM risk assessment under REACH.	**journal article**	**Todd Luxton**	**NRMRL**
Emerging Materials	**Unique characteristics of Metallic ENMs with Respect to Life Cycle, that influence Synthesis, Release from Industrial Processes and Consumer Products, Exposure, and Biological Effects**	There exist considerable data gaps in methods and values for the synthesis, characterization, release and exposure of ENMs associated with the use of these consumer products. This product will consist of several studies focused on metallic ENMs (Ag, Cu, Zn, etc), that cover specific points of release and potential exposure along their life cycle. These will include: classification of synthesis methods, evaluation of releases related to consumer products, and unique characteristics of metallic ENMs both in environmental and biological compartments.	**journal article**	**Kim Rogers**	**NERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Emerging Materials	**Development, parameterization, and evaluation of WASP8 for simulating the fate and transport of nanoparticles in surface waters**	A reliable method is needed to predict concentrations of nanomaterials in surface waters and sediments. To address this need, we are redesigning EPA's Water Quality Analysis Simulation Program (WASP), which currently handles nutrients and organic contaminants, to incorporate nanomaterial-specific processes. The updated model will simulate nanomaterial concentrations in the water column and sediments, and evaluate where nanomaterials are most likely to end up in the environment. This is the first work of its kind to evaluate the spatial and temporal variation of nanomaterial releases into the environment and will allow us to simulate nanomaterial exposure concentrations to humans and wildlife nanomaterials in aquatic systems.	**journal article**	**Chris Knightes**	**NERL**
Emerging Materials	**Development and Application of Functional Assays to Quantify the Release and Effects of Copper Nanomaterials from Consumer Products in Marine Systems**	Very little data exist on the release of copper nanomaterials into marine systems from consumer products treated with this form of nanomaterial. This product will discuss the results of a series of studies examining the amount and form of copper released into marine systems from nanocopper and conventional copper pressured-treated lumber. These results provide information for environmental regulators and managers to assess the fate and effects and risks associated with lumber treated with nanomaterials.	**journal article**	**Rob Burgess**	**NHEERL**
Emerging Materials	**Model relationships between nanomaterial physical and chemical properties, and results of in vitro assays**	QSAR modeling techniques will be implemented to find a relationship between the descriptors of in vitro assays and their experimental responses. The final product of this analysis will be a predictive function to estimate responses when using similar values from the same set of descriptors. The direct impact of this product will be the ability for researchers to predict the response of exposing human cells in vitro to emerging nanomaterials that are comparable in nanostructure to other nanomaterials already studied in vitro. However, the limited scope of these prediction will indicate where more in vitro experiments should be conducted to broaden the range of predictions. In addition, these predictions may help decide when emerging materials need further investigation immediately, and when the need is not as urgent.	**journal article**	**Paul Harten**	**NRMRL**
Emerging Materials	**Cytotoxicity of pristine and gastrointestinal fluid-treated copper nanoparticles in rat and human intestinal cells**	Copper nanoparticles are used as a wood preservative and have electrical applications. Exposure of copper nanoparticles to the gastrointestinal tract may occur from ingesting contaminated food or liquids, hand-to-mouth activity following dermal contact with the particles, or inhalation of the particles followed by their movement up to the trachea by action of the mucociliary tract and subsequent swallowing. In this study we will examine the in vitro toxicity of copper nanoparticles in rat intestinal epithelial cells and a human 3-dimensional intestinal cell model. For this study we will examine pristine and particles that are pre-incubated in gastrointestinal fluid (gastric and intestinal), which may alter the particles. The treatment of the nanoparticles with the fluid may affect their potential cytotoxicity.	**journal article**	**Mike Hughes**	**NHEERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)					
Project	**Product Title**	**Product Description**	**Product Type**	**Product Lead**	**L/C**
Emerging Materials	**Cellular uptake, genomic, biochemical and metabolomic effects of metal and metal oxide nanomaterials**	This product will present results from experiments with metal and metal oxide nanomaterials in human liver (HepG2) cells. Several different aspects will be included such as cellular uptake by ICP-OES analysis and biochemical parameters, several of which are related to oxidative stress. Some genomic and metabolomic work has been performed and some of this is published. The format of the product will range from data base format in some cases to prose summaries or tabular summaries in other cases.	**journal article**	**Kirk Kitchin**	**NHEERL**
Life Cycle & Human Exposure Modeling	**Beta Version Human Exposure Model (HEM) for characterizing exposures of the general population and sensitive subpopulations to chemicals in consumer products**	This deliverable will be the beta version of a web-based software tool, HEM, that generates estimates of aggregate exposures to chemicals from the use of multiple consumer products. Future work under the project includes transition of the model to a publically available version, refinement of different modules within HEM, and expansion of the scope of the model (e.g. inclusion of a wider range of exposure sources including diet, far field sources, additional consumer products, building products, and articles such as furniture and appliances).	**software**	**Kathie Dionisio**	**NERL**
Life Cycle & Human Exposure Modeling	**New models and data that will capture population variability in consumer product and household exposure sources in support of the HEM model**	The deliverable will be comprised of a package of materials including publications, databases, and modular software programs that comprise the fundamental building blocks of the HEM model. Publications will cover novel science that is being developed under the project and is the basis for the modules forming HEM. Topics to be covered in the publications include the use of Agent Based Models (ABMs) to characterize human behavior, updated tools for characterizing product composition, and new methods for the generation of synthetic populations. Databases to support these publications (e.g. databases of demographic information linked to physiological and residential characteristics and to the behavior and activity patterns of the respective individuals) will be included with the deliverable, in addition to the computer code/modules to implement methods described in the publications. These components are the building blocks of the HEM but are of interest to a wider audience of air and chemical exposure researchers in various program and regional offices. Thus, they will be made available as standalone programs that can be used separately from HEM.	**journal article**	**Paul Price**	**NERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Life Cycle & Human Exposure Modeling	**Guidance for Data Quality Assessment for Life Cycle Inventory Data to Improve the Transparency and Interpretation of LCA case studies**	Data quality guidance has been needed for the LCA community for many years to allow a greater understanding of the sources of uncertainty and variability within the inventory and impact assessment phases. It is increasingly important for near-field exposure incorporation into LCA since many near-field sources allow more sophisticated modeling including population groups and exposure pathways. Fortunately, the current techniques are being developed to allow a greater understanding of the probabilistic nature of the data and tools within the project and will allow a propagation of these variabilities and uncertainties, but there are a number of aspects of data quality important to results interpretation that need to be addressed in qualitative ways. This task will provide a guidance report, article(s), LCA software enhancements and associated training materials specifically to address data quality within the development of the inventory side to support LCA data documentation and result interpretation for LCA practitioners. The resulting data quality methods and indicators will be incorporated into the LC-HEM tool to aid in understanding underlying life cycle inventory data quality and guide data quality-related result interpretation.	**journal article**	**Wes Ingwersen**	**NRMRL**
Life Cycle & Human Exposure Modeling	**Library of life cycle inventory for pollution control units / abatement technologies to expedite the generation of LCI**	Near-field exposure models characterize a variety of materials including consumer products which are made in manufacturing plants and recycled or discarded in other facilities that utilize a variety of pollution control units and abatement technologies. The ability of LCA models to rapidly determine accurate life cycle inventories (LCI) under realistic technical constraints for these technologies has been limited or absent in the past. This deliverable will help fill the gap for LCI models which will be useful to the entire LCA community.	**journal article**	**Ray Smith**	**NRMRL**

CSS - FY17 Deliverables (UPDATED 10/27/16)					
Project	**Product Title**	**Product Description**	**Product Type**	**Product Lead**	**L/C**
Life Cycle & Human Exposure Modeling	**Framework for the determination of lineage/genealogy of chemicals to expedite the generation of LCI**	To support automated life cycle inventory generation, there is a need to be able to predict the complete material requirements for the production of a chemical going back to a set of core materials (i.e., crude oil, minerals, ores, biomaterials, etc.). A framework for determining the material requirements for the lineage/genealogy of a chemical will provide a methodology for further automation. The lineage/genealogy of a chemical defines a set of known chemical synthesis pathway steps (e.g., aniline's parents are nitrobenzene, hydrogen, and a Pt catalyst; nitrobenzene's parents are benzene and nitric acid). Once the lineage/genealogy is determined, it's available for defining an LCA study synthesis network (e.g., anytime one uses aniline its parents and grandparents, etc., are available). The existing methodology used by LCA practitioners employs ad hoc research to determine an LCA study synthesis network. The new framework will create a systematic methodology. This deliverable is important to the project since many consumer products are built using similar synthesis pathways, and once the lineage/genealogy is available for one consumer product it can be used for all similar products.	**journal article**	**Ray Smith**	**NRMRL**
Life Cycle & Human Exposure Modeling	**First steps in integrating the use phase of building materials into near-field LCA characterization**	The LC-HEM project is focused on taking the first steps in integrating near-field exposures into LCA. Ongoing research in this project performed by NERL is focusing on exposures to consumer products including personal care products, cleaning products and other non-building related materials within the home. This deliverable presents NRMRL's first steps in integrating the use phase of building materials into near-field characterization includes using the Pharos Building Product Library and various chemical/physical property databases to create a taxonomy of building products. The task will then identify the chemical-product archetypes that have the greatest potential for exposure to humans or releases to the environment. Human exposure pathways considered may include inhalation, ingestion, and dermal contact. The parameters expected to be most important in characterization include: thickness of material, diffusivity of the substance, and the type of material in which the substance is embedded. A journal article explaining the taxonomy development and a database of relevant information for specific chemical-product combinations (and their supporting data) will be created to support future steps of characterizing the potential for impacts from building materials. The database will provide inputs to the exposure and LCA portions of the project.	**journal article**	**Jane Bare**	**NRMRL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Life Cycle & Human Exposure Modeling	**Methods and Data to Characterize Chemical Emissions from Spray Polyurethane Foam**	The goal of this task is to inform and support LC-HEM case study development while meeting OPPT needs for consensus test methods and emissions data for polyurethane products. This task focuses on Spray Polyurethane Foam Insulation (SPFI), a material that is manufactured on-site in residential, commercial, and institutional (school) buildings using a complex mixture of chemical substances of high priority to the Agency and other federal partners. The complex mix of chemicals presents challenges to emissions and exposure characterization and to integration of LC-HEM modeling and rapid exposure assessment methodologies. Life-cycle assessments for SPFI have been conducted by the spray polyurethane industry focusing on the energy-saving performance benefits, with particular characterization of impacts of next generation of blowing agents; however, the LCAs conducted do not consider the health and environmental attributes of the other chemicals in this complex product mixture.	**journal article**	**Mark Mason**	**NRMRL**
Ecological Modeling	**Develop a knowledgebase of xenobiotic metabolism in fish to provide an assessment of similarities and differences in metabolic products across species to reduce ecological risk assessment uncertainties**	This product includes the procurement and coding of pesticide metabolism pathways for several fish species into a searchable electronic database equipped with data evaluation tools. The tools will be used to systematically compare across fish metabolism data and with curated rat metabolism data on an individual chemical basis as well as establishing trends across chemical groups. A journal article will highlight the similarities and differences in metabolic product formation across species and chemicals and therefore provide an assessment of species extrapolation assumptions that are currently applied in ecological risk assessment.	**journal article**	**Rick Kolanczyk**	**NHEERL**
Ecological Modeling	**Benthic invertebrate sediment bioaccumulation tests to improve current models for risk assessment that predict chemical uptake rates, depuration rates and bioaccumulation**	For methodologically challenging compounds with large log KOWs (i.e., > 10), measured biota sediment accumulation factors, chemical uptake rates, and chemical depuration rates are very limited for benthic invertebrates. This product will provide measured values for a series of chemicals with large log KOWs generated using laboratory exposures with Lumbriculus variegatus. These data will be used to evaluate and if needed improve models for predicting these parameters in existing food web models used by the Agency.	**journal article**	**Lawrence Burkhard**	**NHEERL**
Ecological Modeling	**Compilation of amphibian dermal exposure data and its application to the selection of a dermal uptake model as part of the FIFRA pesticide registration amphibian model**	For a number of pesticides, dermal exposure is the primary exposure pathway in amphibians, however, the EPA does not currently have a method for estimating amphibian dermal exposure. This was mainly due to a lack of quantitative exposure studies for this pathway. This manuscript product will collect data from amphibian exposure data collected and published by ORD and outside the EPA to synthesize to evaluate and recommend an exposure model for use in higher tier amphibian assessments.	**journal article**	**Tom Purucker**	**NERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Ecological Modeling	**Population modeling tools to support pesticide risk assessment.**	These products show the contributions that population modeling can have to inform ecological risk based decision making for pesticide registration. They include an integrated version of the TIM/MCnest model that allows for acute and chronic (reproductive) effects on birds to be considered simultaneously and will weight them appropriately according to the life history of the species. It also includes manuscripts documenting 1) parameter estimation and sensitivity analysis for the EPA/USDA collaboration on honeybee colony simulation modeling, 2) the final integrated TIM/MCnest model and enhancements to MCnest to handle temporally variable model parameters, and 3) periodic matrix and internal dose models for estimating population effects from time-varying exposure. Finally, the product will include a working version of the HexSimPLE simulation modeling framework.	**journal article**	**Matt Etterson**	**NHEERL**
Ecological Modeling	**Evaluating Bioaccumulation and AOP effects of selected Methodologically-Challenging Chemical Methods via testing Adverse Outcome Pathway predictions using genomics and standard laboratory endpoints**	This product will include 1 or more journal articles that focus on the (1) observed bioaccumulation and biological effects of a selected methodologically-challenging chemical, bis (2-ethylhexyl)-2,3,4,5-tetrabromophthalate (CAS 26040-51-7), and (2) the adverse outcome pathways affected by exposure to this compound, inferred using genomic data.	**journal article**	**Diane Nacci**	**NHEERL**
Ecological Modeling	**Sensitivity analysis and comparative evaluation of growth and fecundity parameters tosupport development of amphibian translator models**	Development of an amphibian translator will identify defensible approaches that can be used to translate surrogate fish toxicity test data into ecologically relevant endpoints for anuran larvae (tadpoles). Research will include both an evaluation of using fish toxicity test data as a surrogate for amphibian toxicity and translation of laboratory endpoints to those of ecological relevance across taxa. Supporting sensitivity analyses will provide population-level comparison of similar growth and fecundity effects on species with varying life history traits.	**journal article**	**Jill Awkerman**	**NHEERL**
Ecological Modeling	**Trait-based population models for evaluation of chemical, ecological, and demographic traits that influence species vulnerability to pesticide use for initial detection of sensitivity in novel chemical/species exposure scenarios**	A framework for trait-based ecological risk assessment in ecotoxicology outlines three primary components as influential factors in determining species vulnerability: inherent sensitivity, external exposure, and population sustainability. Our exploratory research on trait-based risk assessment will use knowledge about chemical properties, exposure patterns, and species life history to develop a classification scheme for vulnerability for use in Tier 1 risk assessments.	**journal article**	**Jill Awkerman**	**NHEERL**

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Ecological Modeling	Quantitative comparison of exposure predictions from the Spatial Aquatic Model to pesticide surface water monitoring data collected in the Central Valley of California	This manuscript will quantitatively compare ecological exposure predictions from the Spatial Aquatic Model to pesticide surface water monitoring data collected in the Central Valley of California. This model has undergone external Science Advisory Panel review in preparation for future use in EPA pesticide registration and endangered species effects assessments. This application is important due to the rich resources available in the Central Valley for data-driven algorithm selection and model calibration/evaluation activities. ORD has cultivated a number of research collaborators in this area in addition to the available detailed records of pesticide application, timing and amounts. This combination affords multiple opportunities to comparing model predictions to field observations at numerous pesticide, location, and time combinations.	journal article	Tom Purucker	NERL
Ecological Modeling	Empirically-based modeling and mapping of exposure risk for aquatic species	Risk managers would benefit from modeling tools that facilitate probabilistic assessment of potential exposures at the landscape or watershed scale. This product will detail a modeling framework that can harness empirical data and GIS resources to produce maps of the expected co-occurrence of contaminants and species, while accounting for uncertainty under the Bayesian paradigm. An example application will be provided that demonstrates the use of existing aquatic bioassessment data to generate “screening-level” maps of risk under this framework. Moreover, the framework will be extendable to more complex parameterizations that, given sufficient data, could afford a finer resolution of exposure risk across time and space.	journal article	Roy Martin	NERL
Ecological Modeling	Environmental DNA (eDNA) surveillance to determine spatial distribution and occupancy of Endangered Aquatic Species	Risk assessors and environmental managers need efficient and non-invasive tools to monitor populations of sensitive, threatened, and endangered species. This product provides a detailed eDNA sampling protocol designed for detecting threatened and endangered aquatic species. The utility of this methodology will be demonstrated through its application to real-world listed species.	journal article	Eric Waits	NERL
Ecological Modeling	HexSimPLE case studies to illustrate the application of this model for FIFRA and ESA that involve the use of EFED data	This product will consist of one or more applications of the HexSimPLE rapid assessment modeling toolkit to wildlife species-landscape-stressor systems of interest to EFED. Model detail and sophistication will depend on the amount and quality of data provided to ORD by EFED.	model	Nathan Schumaker	NHEERL

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Ecological Modeling	HexSim modeling simulation framework manuscript	HexSim is the most advanced IBM (individual-based model) designed for simulating wildlife population dynamics and trends. HexSim development began in 2006 and the model reached maturity in 2016 with the release of version 4.0. This manuscript will describe HexSim's design and features, and discuss many model use-cases.	journal article	Nathan Schumaker	NHEERL
Ecological Modeling	An integrated modeling framework for spatially explicit avian risk assessment using TIM, MCnest, and HexSim	This product will provide a standard workflow for parameterizing TIM, MCnest, and HexSimPLE for conductng pesticide risk assessments. The model will rely on standard data available under FIFRA registration requirements and will provide projections of relative impacts of pesticdes on birds under different exposure condtiions. The working model will form the basis for technology transfer to EPA/OPP.	model	Matt Etterson	NHEERL
Ecological Modeling	Framework for applying population models for effects assessment of endangered species exposed to pesticides	The manuscript will provide a framework for selecting and applying population models of varying complexity in ecological risk assessment.	journal article	Sandy Raimondo	NHEERL
Demonstration & Evaluation	Identification of reference chemicals necessary to evaluate predictive models of androgen receptor (AR) activity	While the Agency has employed ToxCast and ExpoCast data/models to prioritize chemicals based on estrogenic potential, new data and models are still needed for androgen disrupting chemicals. This research requires development of predictive models as well as reference compounds to evaluate these models. A novel approach to identifying reference compounds for high throuhgput assays was delivered in FY16. Using this novel appraoch, this manuscript will be a case study to identify reference chemicals for AR (androgen receptor) assays using this novel approach.	journal article	Richard Judson	NCCT
Demonstration & Evaluation	Evaluation of steroidogenesis high-throughput screening methods using reference chemicals	A current weakness in predicting androgenic activity of chemicals is a lack of data on steroidogenic pathways. A novel model to predict the impact of chemicals on steroid hormone synthesis and catabolism. This product will be used to reduce uncertainties in prioritization of chemicals under the Endocrine Disruptor Screening Program (EDSP)based on potential endocrine activity.	model	Richard Judson	NCCT

CSS - FY17 Deliverables (UPDATED 10/27/16)

Project	Product Title	Product Description	Product Type	Product Lead	L/C
Demonstration & Evaluation	**Decision support dashboard for integrating traditional and alternative data related to chemical properties, hazard, and exposure to support chemical safety decisions**	A huge challenge in managing risk of chemicals is the lack of access to hazard and exposure data for thousands of chemicals currently in commerce. This project will develop an internally accessible web-based platform that integrates high- throughput, exposure, and curated physiochemical and structural information. The software will provide risk estimates with associated uncertainties for use by program offices, regions and outside stakeholders.	**software**	**Tony Williams**	**NCCT**
Demonstration & Evaluation	**Development of read across models to provide toxicity predictions for hundreds of chemicals based upon structural features**	A major problem with existing read-across methods is the reliance on subjective assessments off structural similarity and predictive accuracy. This research effort will develop novel models that employ chemical structures and physical-chemical properties to generate read-across predictions with quantitative measures of model uncertainties. Use of this model, generalized read-across (GenRA), will increase confidence in the use of read-across approaches in Agency risk decisions.	**model**	**Imran Shah, Grace Patlewicz**	**NCCT**
Demonstration & Evaluation	**Estimating uncertainty in potency from in vitro high-throughput screening assays**	This article will describe an objective framework to estimate uncertainty in high throughput assays. This article will provide measures of confidence and uncertainty to determine fitness-for-purpose for different EPA actions. This product will provide risk assessors with uncertainty quantification that should increase confidence in risk decisions.	**journal article**	**Matt Martin, Richard Judson**	**NCCT**