



Research Strategy 2020-2024

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Executive Summary

The American Chemistry Council's Long-Range Research Initiative (LRI) is designed to address the challenges facing the industry in chemical safety assessment. The LRI Research Strategy 2020-2024 outlines an agenda that complements ACC's advocacy priorities, particularly those focused on successful implementation of the new requirements in TSCA as a result of the Frank R. Lautenberg Chemical Safety for the 21st Century Act. This research agenda focuses on advancing the scientific tools to increase efficiency and predictiveness for chemical safety evaluations for applications in TSCA (both new and existing chemicals), product stewardship and the value chain, by concentrating on three key areas:

- Many chemicals in commerce still lack publicly available exposure data for conditions of use. This impedes the effective implementation of TSCA activities to integrate hazard and exposure information and can lead to reliance on worst case exposure assumptions that create erroneous estimates that tend to overstate risks.
 - To overcome such limitations requires development, demonstration and uptake of scientifically sound exposure tools that support tiered approaches, appropriately address workers, consumers and sensitive subpopulations, and ecological receptors.
 - Accordingly the LRI Research Strategy 2020-2024 focuses on developing exposure tools necessary to 1) quickly and reliably provide exposure information to enable risk-based prioritization of 20,000 – 30,000 chemicals under TSCA as low priority of high priority for risk evaluations; b) accurately assess risks of high priority chemicals under TSCA; and 3) avoid unwarranted product characterization and de-selection by customers based on hazard considerations alone.
- New approach methods (NAMs) to evaluate the biological activity of chemicals are rapidly advancing. TSCA now requires use of such methods in lieu of traditional animal toxicity tests when they can provide information of equivalent or better scientific quality and relevance for assessing risks. EPA has just launched a strategic plan to develop and integrate NAMs for decision making under TSCA. In addition, The EPA Administrator in September 2019 announced an initiative to “aggressively reduce animal testing throughout the agency,” by setting goals to reduce EPA's requests for, and funding of, mammal studies by 30 percent by 2025, and for EPA to eliminate all mammal study requests and funding by 2035.
 - Accordingly, the LRI Research Strategy 2020-2024 addresses this challenge with a concentration on collaborative research to actualize *in silico*, *in vitro* and tiered testing and assessment approaches by focusing on developing / improving NAMs based on computational methods, high-throughput and high content assays, and *in vitro* cell based assays to generate relevant biological activity data that can be used to more efficiently evaluate the safety profiles of chemicals with respect to human health and ecological effects.
 - Once sufficient confidence is established in these NAMs, they can be applied to generate more rapid, cost effective and less animal intensive data for chemical safety determinations in the context of problem formulation.

- Matching these new tools and methods up to the specific decision contexts — such as candidate selection for prioritization, or prioritization and screening, or in-depth risk evaluations based on mode of action — and demonstrating scientific confidence for each of these decision contexts is needed.
- Under the new TSCA, data needs for toxicity information are expected to arise as EPA focuses on upcoming sets of priority chemicals. While new approach methods (NAMs) are envisioned to be capable of meeting many of these data needs, improved tools are still needed to enable effective integration of biological activity data with exposure information at each decision node to support 21st century risk-based decision making.
 - Significant challenges exist in applying such approaches to new chemicals that lack or have little toxicity information, and to complex mixtures (UVCBs, which comprise approximately 25% of the active TSCA inventory).
 - Consequently, the LRI Research Strategy 2020-2024 concentrates on improving computational approaches to generate surrogate hazard information in lieu of conducting animal toxicity studies in a manner that promotes the integration of hazard, mode of action and exposure to improve the predictiveness and efficiency of assessing risks from chemicals.
- The rapid pace of development and implementation of new approaches to developing bioactivity data (hazard) and exposure information makes it hard, if not impossible, for ACC members to keep abreast of strengths, limitations, and beneficial applications of such methods for product stewardship and regulatory decision making.
 - This pace of generation of NAMs has outstripped the ability of many ACC panels and member companies to understand the strengths and limits of such methods. This is limiting ACC members' effective engagement in venues where such NAMS are being used (e.g., by EPA ORD in developing multiple categories for PFAS). And such a lack of knowledge can also impede the update and use of these members by ACC members in their new chemicals and product stewardship programs.
 - Although there are many opportunities, through scientific workshops and meetings, for member company experts to learn about these new methods, such venues typically focus on the underlying science and not on “what these tools and methods mean” for application in the chemical sector (e.g., for TSCA).
 - Consequently, the LRI Research Strategy 2020-2024 includes knowledge transfer activities that will be specifically designed to meet the needs of ACC panels and members to understand these advanced approaches so that they can be applied to efficiently and effectively address the chemical hazard, exposure and safety challenges they face.

The LRI-developed methodologies will contribute to the requirements for chemical risk evaluations under the new TSCA. They will also serve as a resource for American Chemistry Council members to address their own product issues regarding hazard, exposure, and risk evaluations; they can support company product stewardship efforts (including responding to ill-founding allegations), new product development, and sustainable design of new materials.

LRI research has laid an important foundation for success. Collaborations between LRI investigators and scientists from federal governmental agencies during the past five years have been an essential contribution of the LRI program. These collaborations have facilitated acceptance of LRI outcomes in the regulatory science community, in TSCA modernization and are having a positive influence on improving chemical safety assessments today.

The LRI is the chemical industry's investment in research that affirms its commitment to product safety and stewardship. Through the LRI, the industry is actively collaborating and engaged in scientific research that addresses current advocacy challenges and that contribute to the transformation of chemical safety assessment. The LRI program, in short, is an essential component for ACC advocacy success.

I. ACC LRI: Addressing Challenges to the Chemical Industry

Around the world, the chemical industry faces multiple challenges regarding chemical risk assessment. Scientific exposure and toxicological research is essential for addressing these challenges and for providing the basis for sound decision making regarding the safe use of chemicals. The Long-Range Research Initiative (LRI) Program at the American Chemistry Council (ACC) is industry's investment in research that affirms its commitment to determine the safety of its products and supports responsible product stewardship. The LRI research program advances chemical safety assessment through innovative approaches and methodologies for evaluating chemicals and products. ACC member companies can apply these new approaches and methodologies as part of their own efforts to address issues in hazard, exposure, and risk assessment for their products and to meet the public demands for product safety information.

The research supported by the LRI is directly relevant to chemical management and advocacy initiatives within the ACC. This specifically includes addressing some of the most significant challenges for implementing the modernized TSCA.

One of industry's goals for the modernized TSCA is to restore public confidence in the safety of chemical products as a result of affirmative findings of the safety of chemicals for their conditions of use by EPA. At the present time, EPA is in the process of releasing draft risk evaluations of the first 10 high priority substances, and EPA late in 2019 identified the next 20 high priority substances for risk evaluations. In addition, in February 2020, EPA finalized the first 20 low priority substances under the new TSCA. Although these numbers of chemicals are the minimum mandated by the statute, such a pace will not meet the objective of restoring confidence in the safety of chemical products. Hence, one of the grand science and research challenges is to develop and build confidence in rapid risk based screening methods that can be used for risk-based prioritization of the 20,000 – 30,000 chemicals on the existing TSCA inventory to permit EPA to more rapidly identify low risk substances for which comprehensive risk evaluations are not warranted at this time.

Under the new TSCA, EPA is required to make affirmative risk-based decisions in approving pre-manufacturing notices for new chemicals. In applying this authority, it is critical that EPA focus on chemicals and effects of concern for a given exposure, and focus on the information most relevant to improving the utility of the risk assessment for decision-making, so as to avoid unnecessary use of resources and delays in approving PMNs. The LRI 2020-2024 Research Strategy is designed to help address this situation by 1) improving understanding of consumer and worker exposures by building confidence in suitable exposure models 2) developing and building confidence in new approach toxicity evaluation methods (NAMs), such as computational approaches and 21st century *in vitro* assays, that are more relevant, and rapid and cost effective than traditional lab animal tests.

The modernized TSCA gives EPA new authority to require toxicity testing by simply issuing test orders directly to manufacturers. This is a more rapid procedure than in the past when EPA had to issue a formal test rule. Although this test order authority had not yet been exercised under the new TSCA, there is no doubt that it will be used in the months and years ahead. For chemicals with sparse toxicity data and for complex substances (UVCBs), EPA's initial evaluation may reveal significant and extensive gaps in traditional animal toxicity testing data sets. The LRI 2020-2024 Research Strategy is designed to provide methods and approaches to be used to address relevant toxicity and exposure information needs. This research is intended

to provide scientifically sound and credible information in a timely and targeted manner to inform chemical risk management decisions by developing and building confidence in hypothesis-based integrated approaches for tiered testing and assessments in lieu of traditional empirical animal toxicity data. This tiered and fit for purpose (align with the decision context) approach is defined by acceptable risk levels, beginning with least costly, less refined/complex methods (e.g., *in silico*) and proceeding, if warranted, to more refined/complex methods (e.g., 21st century non-animal tests), with knowledge of exposure being integrated at each tier to enable risk-based determinations.

Current challenges to be addressed in the LRI program under the 2020-2024 strategy include:

- Lack of publicly available exposure data for conditions of use, including exposures to workers, consumers and sensitive subpopulations.
- Increasing public demand for safe products, and the insistence by some groups to rely solely on hazard data for decision making.
- The need for scientifically solid methods to conduct risk-based prioritization of the 20,000 – 30,000 chemicals on the existing TSCA inventory to permit EPA to more rapidly identify low risk substances for which comprehensive risk evaluations are not warranted at this time.
- The importance of developing and applying tiered evaluation approaches in TSCA that use new approach methods (in place of traditional animal toxicity tests), for both human health and ecological effects.
- The need for scientific tools to enable integration of biological activity data with exposure information at each decision node within a tiered testing framework to support 21st century risk-based decision making.
- The requirement to establish scientific confidence in new approach methods for specific uses, including methods to address complex substances (e.g., UVCBs).
- The need to fill the knowledge gap experienced by ACC panels and members created by the rapid pace of NAM development.

As noted, the assays and risk-based methods developed through LRI research can be applied by specific panels in ACC's Chemical Product and Technology Division (CPTD) and the Plastics Division, and in ACC's Sustainability and Market Outreach program. In each of these areas, the need for high quality and reliable exposure modeling tools and approaches is paramount to ensuring that risk, and not hazard alone, is the basis for decision-making about chemicals, whether by regulators, retailers, or the general public. In addition, each of these programs face the challenge of understanding and communicating in a risk context the deluge of "hazard and effects" data from new approach methods, such as high throughput screening, transcriptomics, and *in silico* prediction models. In the months and years ahead, ACC members and CPTD panels will likely find themselves in a position of needing more up to date hazard and exposure information to support risk-based decision making in TSCA and for product stewardship. The LRI research projects outlined in this generate LRI Strategy 2020-2015 are designed to meet many of these needs.

The LRI Research Strategy 2020-2024 was developed by the ACC's LRI Strategic Science Team (SST), which provides oversight and direction for the program. The SST's deliberations to develop the LRI Research Strategy 2020-2024 were informed by presentations and discussions with the groups listed below; all of whom provided valuable insights for shaping this document.

- Members of the ACC Board Chemical Management Committee;
- ACC staff from the Chemical Product and Technology Division and the Plastics Division;
- ACC staff from the Sustainability and Market Outreach program;
- ACC staff from the Regulatory and Technical Affairs Department;
- LRI investigators, including those from ScitoVation; and
- Scientists from the EPA's Office of Research and Development (National Exposure Research Laboratory and National Center for Computational Toxicology, and National Center for Environmental Research), and from EPA's Office of Chemical Safety and Pollution Prevention (Office of Pollution Prevention and Toxics and Office of Pesticide Programs).

II. LRI Research Strategy 2020-2024: Research to Support Advocacy Success

The LRI Research Strategy 2020-2024 integrates three research areas that focus on developing solutions for the challenges facing the chemical industry. This section explains the basis for selection of the three research areas, the proposed research project areas, and the potential value of the research for the chemical industry.

The overwhelming focus of the LRI Research Strategy 2020-2024 is to develop the tools, methods and data needed to support risk-based prioritization and risk evaluations for implementation of the new TSCA. These include:

- The need for a tiered method to generate exposure information for workers, consumers and sensitive subpopulations for conditions of use to enable TSCA to make credible risk-based decisions.
- The need for scientifically sound, widely accepted risk-based evaluation procedures for pre-priority setting / priority setting that will permit rapid, cost-effective method(s) to identify higher priority substances from those chemicals of lower concern.
- The need for improved tools for the new chemicals program, including new computational tools and *in vitro* methods to identify potential hazards (such as lung effects), and improved exposure models.
- The need for new and improved methods to group chemicals in categories based on understanding of biological profiles, not just chemical structure and traditional animal toxicity data. Read across inference can then be applied to limit the need / requirement for additional testing.
- When it's determined that there's a need for additional toxicity data (e.g., when EPA issues testing orders under the new TSCA), integrated approaches for tiered testing and

assessments should be available to use by ACC members in lieu of traditional animal toxicity tests. Such an approach needs to 1) be tiered and fit for purpose (align with the decision context), 2) begin with least costly, less complex *in silico* methods and proceed, if warranted, to more complex tests 3) uses 21st century non-animal tests that provide scientifically relevant data; and 4) integrates knowledge of exposure at each tier to enable risk-based determinations if the next level of testing is warranted.

- The need for new and improved methods to understand mode of action and dose response modeling that can be compared to default approaches to ensure best available scientific approaches are used for the most advanced safety assessments conducted under TSCA.
- The need for improved, best available science methods for conducting weight of evidence determinations for persistence and bioaccumulation.

These tools methods and data can also be applied by ACC panels and ACC member companies for product stewardship. It is also envisioned that some of the tools and approaches, such as Thresholds of Toxicological Concern and consumer exposure modeling, could be adopted for sustainability and value chain uses.

Thus, major projects under the program are oriented toward:

- Further development, verification and use of predictive exposure models for consumers, workers and sensitive subpopulations.
- Developing and improving fit-for-purpose chemical safety testing technologies assays and tiered approaches to testing and assessment.
- Improving approaches that integrate hazard, mode of action and exposure to support weight of the evidence risk-based decision making.

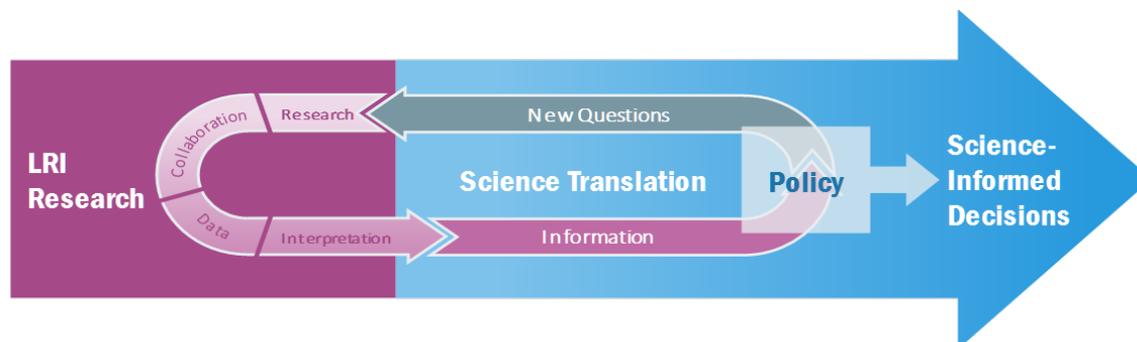
The LRI Research Strategy 2020-2024 also aims to leverage the valuable collaborative relationships amongst ACC scientists, the LRI investigators, and scientists from the federal institutes and regulatory agencies. These relationships have been critical in facilitating acceptance of outcomes from LRI research in chemical safety assessment by the broader scientific community and in setting the stage for use in the modernized TSCA. These collaborations have been and will continue to be integral for LRI research for innovations in chemical testing technologies and exposure science. In short, the LRI program has:

- Leveraged ACC research funds through strategic collaborations.
- Optimized use of financial resources for research in areas of mutual interest for chemical safety assessment with governmental agencies.
- Fostered transparency of information related to both methods development and data generation.

The LRI program thus helps demonstrate the industry's value as a constructive partner for providing credible scientific research that focuses on solutions and ensure that industry plays an important contributing role and makes a difference in the development and implementation of new technologies for chemical safety assessment.

The LRI model for success is depicted in Figure 1. The goal is for LRI to provide timely and relevant research that can be translated into policies and practices for product stewardship and regulatory decision making.

Figure 1. The LRI Model: Science to Inform Policy



III. The Four Areas of the 2020-2024 LRI Research Strategy

A. Advancing the Understanding of Exposures to Promote and Enhance Risk-Based Decision Making (Consumers, Workers, Sensitive Subpopulations, Eco/Environment)

The absence of exposure data for conditions of use for the majority of chemicals in current commerce is a significant obstacle that limits the ability to conduct risk-based prioritization and credible in-depth risk assessments. Under the new TSCA, risk-based regulatory approaches are being implemented for new chemicals, for prioritizing existing chemicals and for conducting safety evaluations on high propriety substances. In each case, exposure information is a key element. In the absence of verified exposure information, worst case exposure assumptions may be used, and this increases erroneous estimates of risks.

To overcome such limitations requires development, demonstration and uptake of scientifically sound exposure tools that support tiered approaches, appropriately address workers, consumers and sensitive subpopulations, and ecological receptors. The LRI Research Strategy 2020-2024 will address current gaps in exposure data through several approaches.

Research Objectives

- Develop and improve predictive models for generating exposure estimates. Exposure estimates will be used for developing a practical and useful tiered framework for prioritization of chemicals to enable 1) risk-based prioritization of 20,000 – 30,000 chemicals under TSCA to permit low risk substances to be rapidly de-prioritized; and 2) more accurate exposure estimates for in depth safety evaluations of high priority substances under TSCA.
- Increase information about consumer exposures through innovative approaches to collate data from industry resources regarding chemical properties as well as product composition and use information that will comply with concerns about confidential business information.

- Through this research, develop collaborations with expert stakeholders in occupational exposure (e.g., EPA, OSHA, NIOSH, industry, etc.) and exposure modeling to improve knowledge of, and methods for, quantifying worker exposure for use in pre-prioritization, new chemical evaluations and in depth risk evaluations of high priority substances.

The ACC LRI 2020-2024 exposure science research project areas are summarized in Table 1. The objectives, specific activities, milestones and deliverables for each project will be developed by the ACC LRI Strategic Science Team (SST). Each project is monitored by a Project Monitoring Team, comprised of one or more ACC LRI SST members and where warranted, additional subject matter experts (preferable drawn from ACC member companies). Projects are fully evaluated by the SST at least once per year, and adjustments in scope are made accordingly.

Value to the Chemical Industry

- LRI research can verify and refine exposure models that can be used to produce exposure estimates for TSCA and product stewardship assessments of the potential health and environmental risks from chemicals that are the basis for concerns about industry’s products, both for new and existing chemicals.
- LRI applications of tiered predictive exposure models support efficient and cost-effective generation of exposure estimates for workers, consumers, subpopulations and environmental receptors for TSCA with sufficient precision to support prioritization and safety decisions and also decrease the likelihood of premature decisions about chemical substances based on hazard data alone. This information is relevant to regulatory determinations, marketplace product defense, and company product stewardship and research efforts.
- Exposure science research can accelerate risk-based evaluation of alternative chemicals and green chemistry products by more rapidly identifying those new chemical products and processes that meet safety criteria and support sustainable chemical products design.

Table 1. Advance Understanding of Exposures to Promote and Enhance Risk-Based Decision Making (Consumers, Workers, Sensitive Subpopulations, Eco/Environment)

Project Name	2020	2021	2022	2023	2024
Ex2019: Advance High Throughput Exposure Modeling (complete 2018-2020 projects)					
Ex1: Case examples applying tiered exposure approaches in risk evaluations (human & eco)	(RfP Development)				
Ex2: Improve Exposure Assessment Models Inputs: Composition, Activity Patterns	(RfP Development)				

B. Improving Chemical Safety Testing Technologies: Developing Fit-for-Purpose Assays and Advancing Data Interpretation

New approach methods to evaluate the biological activity of chemicals are rapidly advancing. TSCA now requires use of such methods in lieu of traditional animal toxicity tests when they can provide information of equivalent or better scientific quality and relevance for assessing risks. EPA is implementing a strategic plan to develop and integrate NAMs into decision making under TSCA.

Accordingly, the LRI Research Strategy 2020-2024 contributes to EPA's strategic plan with a concentration on collaborative research to actualize hypothesis-based tiered testing and evaluation approaches by focusing on developing and implementing computational methods, high-throughput and high content assays, and *in vitro* cell based assays in a manner that supports the appropriate use and integration with exposure information to promote informed risk-based decision making.

The LRI Research Strategy 2020-2024 continues work begun in previous years to apply current innovations in testing technology and leverage emerging technologies.

Research Objectives

- Design and evaluate the performance of the next generation of fit-for-purpose assays to address public health concerns about chemicals. The goal is to develop specific assays that can be used in a tiered manner for screening chemicals that will consider the relevant chemical properties of concern as well as metabolism of chemicals.
- Develop and evaluate approaches that use relevant organotypic cell-based assays and high content endpoints to generate dose-response data for deriving points of departure that can be used with *in vitro* to *in vivo* extrapolation to enable risk-based decision making. Such an integrated approach to testing and assessment would be used in lieu of conducting traditional animal tests.
- Develop confidence in transcriptomics methods and high throughput phenotypic imaging for identifying specific and non-specific modes of action and points of departure for priority setting and screening. Comparing such results to existing adverse effects data will provide context for interpreting the transcriptomics data – in a way readily understandable to government regulators and ACC members.

The ACC LRI 2020-2024 chemical safety technologies research project areas are summarized in Table 2. The objectives, specific activities, milestones and deliverables for each project will be developed by the ACC LRI Strategic Science Team (SST). Each project is monitored by a Project Monitoring Team, comprised of one or more ACC LRI SST members and where warranted, additional subject matter experts (preferable drawn from ACC member companies). Projects are fully evaluated by the SST at least once per year, and adjustments in scope are made accordingly.

Value to the Chemical Industry

- Innovations in fit-for-purpose chemical testing will expedite new product development, sustainable design of new materials, and development of new chemical solutions by shortening testing times and increasing cost efficiencies.
- LRI research in new chemical testing technologies can be a key resource for ACC companies and EPA to address potential requirements under the new TSCA re and provide an important complement to ACC's ongoing risk assessment reform advocacy. This research will also be an important resource for other regulatory authorities (e.g., Health Canada, ECHA, etc.).
- Once sufficient confidence is established in these methods, they can be applied to generate more rapid, relevant and predictive, cost effective and less animal intensive data for chemical safety determinations.

Table 2. Improving Chemical Safety Testing Technologies: Design Fit-for-Purpose Assays and Advance Data Interpretation

Project Name	2020	2021	2022	2023	2024
ST1. Lung Effects: Next Generation of Fit-for-Purpose Assays					
ST2. Liver Toxicity: Next Generation of Fit-for-Purpose Assays					
ST3. High throughput Transcriptomics to Assess Specific Modes of Action and Non-Specific Types of Toxicities					
ST4. Evaluating New Technologies: Human Cells Tissue Chips (including metabolic competent cells)					
ST5. Fit-for-Purpose Ecotoxicology Cell-Based Assays and Prediction Models (Eco assays, Species Extrapolation, IATAs, etc.)	(RfP Development)				

C. Improving Approaches to Integrate Hazard, Mode of Action and Exposure to More Efficiently and Precisely Assess Potential Risks from Chemicals

Increasing public demands for information about product safety are being driven by ongoing media reports about epidemiological studies that link detection of chemicals in the body to a variety of adverse health effects, such as obesity and diabetes. In the absence of adequate information on hazard and exposure, as well as the dose-response relationships underlying adverse effects, to address these claims, retailers and product manufacturers are opting to de-select certain chemicals in products, typically without a sound scientific basis formulated on risk.

Over the last 10 years developments in chemical testing technologies have rapidly advanced, resulting the generation of unprecedented amounts of data on biological activity of chemicals in a myriad of test systems. Research funded by the LRI during the past decade has been

fundamental in developing innovative tools that link exposure/dose and hazard and address the public's concerns about risks from chemicals. These tools are based on life stage physiologically based pharmacokinetic (PBPK) models that were developed through LRI support initially at the Hamner Institutes for Health Sciences and more recently at ScitoVation.

PBPK models are designed to consider how chemicals taken into the body are distributed and metabolized and then result in the chemical concentrations that are measured in blood, tissues, and other fluids. The *In Vitro* to *In Vivo* Extrapolation (IVIVE) method, using PBPK modeling, was pioneered by LRI-supported research. IVIVE allows the concentration of a chemical that causes effects in *in vitro* systems to be converted to an equivalent external exposure. This can then be compared to predicted exposure levels to enable the results of *in vitro* assays to be interpreted in a risk context of human exposure. Over the last few years IVIVE has been successfully applied in numerous contexts and has recently been included as an integral part of EPA's strategic plan (issued in June 2018) for developing new approach methods (non-animal testing) for TSCA.

Building upon this successful approach for integrating hazard, mode of action and exposure information, the LRI Research Strategy 2020-2024 outlines research to advance additional integration approaches in several project areas.

Research Objectives

- Complex substances (UVCBs) comprise approximately 25% of the TSCA inventory, but advanced 21C approaches to profile biological activity, estimate exposures and integrate this information to enable risk-based decision making have yet to be developed and accepted.
- Improve approaches for Read Across for complex substances to achieve the vision of risk-based safety evaluation of these substances under the new TSCA. Improve computational approaches and other advanced methods for rapid risk-based screening for priority setting in TSCA through collaborations, including using PBPK models to derive threshold of toxicological concern (TTC) values using an internal exposure metric (e.g. concentration in blood, area under the curve) which accounts for metabolism and enables route-to-route extrapolations.
- Carry out an education and outreach program to facilitate knowledge transfer of advanced, new assessment methods, exposure models and tiered testing and risk assessment approaches to ACC members to promote application in product development and product stewardship.

The ACC LRI 2020-2024 risk assessment tools integration research project areas are summarized in Table 3. The objectives, specific activities, milestones and deliverables for each project will be developed by the ACC LRI Strategic Science Team (SST). Each project is monitored by a Project Monitoring Team, comprised of one or more ACC LRI SST members and where warranted, additional subject matter experts (preferable drawn from ACC member companies). Projects are fully evaluated by the SST at least once per year, and adjustments in scope are made accordingly.

Value to the Chemical Industry

- LRI research in use of innovative data streams to develop biological profiles of complex substances will provide the methods needed to advance assessment of risks from exposures to these substances without requiring conduct of extensive lab animal testing. Improved approaches using computational methods, such as Read Across and internal TTC values, for risk-based prioritization of 20,000 – 30,000 chemicals under TSCA will permit low risk substances to be rapidly de-prioritized.
- Improved risk-based methods to prioritized values can be used to fill toxicity testing data needs without requiring any additional lab animal testing.
- Through education and outreach program to facilitate knowledge transfer of advanced, new assessment methods, exposure models and tiered testing and risk assessment approaches to ACC members to promote application in product development and product stewardship.

A proactive education program is needed to help ACC members become proficient in applying these new tools to enable how they can be used in support of their company’s needs for chemical safety evaluations under TSCA and product stewardship.

Table 3. Improving Approaches that Integrate Hazard, Mode of Action and Exposure to Assess Risks from Chemicals

Project Name	2020	2021	2022	2023	2024
INT1. Improving Safety Assessment Methods for Complex Substances / UVCBs/ Mixtures	(RfP Development)				
INT2. Improving Sources of Data and Technologies Slated to be Used by EPA for Read Across, RapidTox and new proposed approach to prioritize in TSCA	(RfP Development)				
INT3. Develop a Framework for Biologically-based AOPs and Case Examples	(RfP Development)				
INT4. Improving TTC Methods for Inhalation and Dermal Routes (via the internal TTC)					

D. Transferring Knowledge of New Approach Methods (NAMs) to ACC members and ACC Panels to Catalyze Uptake and Use of NAMs

Currently, it is very challenging for ACC panels and many member company scientists to understand strengths, limitations and beneficial applications of NAMS and new exposure methods for product stewardship and regulatory decision making. Typically, scientific venues such as professional society meetings don’t focus on “use of these tools and methods for TSCA or product stewardship.”

Research Objectives

Design and implement a proactive education program to help ACC members and ACC panels become proficient in applying NAMs and other new tools in support of their needs for chemical safety evaluations under TSCA and product stewardship.

The ACC LRI 2020-2024 knowledge transfer project areas are summarized in Table 4. The focus areas for 2020-2022 were selected by the ACC LRI SST with input from the ACC HPSP and CPTD programs. The focus areas are those envisioned to be most important in terms of their readiness for use in TSCA, and product stewardship related to TSCA.

The education and outreach efforts will go well beyond simply presenting webinars. For example, work products may include development of user guidelines, instructional web videos, and hands-on webinar-based training exercises. The ACC LRI has developed such approaches for the Prediction Analytic Toolkit, and will build from this success.

This program will include metrics to measure effectiveness and impact. For the initial four focus areas, such assessments will be conducted in 2021. The program will be fully evaluated during the third/fourth quarter of 2021 and revised as needed. It is for this reason that a placeholder has been inserted in Table 4 for 2022-2024. Again, the objectives, specific activities, milestones and deliverables for each project will be developed by the ACC LRI Strategic Science Team (SST).

Table 4. Knowledge Transfer to ACC Members and ACC Panels

Project Name	2020	2021	2022	2023	2024
EDU1. Threshold of Toxicological Concern (a computational NAM that can be used to fill toxicity data gaps w/o add'l animal testing)					
EDU2. PLETHEM (an open source PBPK model that can be used for forward dosimetry, development of BEs, IVIVE, etc.)					
EDU3. ToxCast User Guide (a step by step guide on how to access, download and evaluate EPA's ToxCast data - approximately 6,000 substances run in over 300 assays)					
EDU4. NAMS: New Approach Methods (TSCA requirements for NAMs, available / soon to be available NAMs, EPA NAMS strategy, EPA's current & future uses of NAMs, etc.)					
EDU5. Placeholder (potential focus areas may include toxicogenomics points of departure, human on a chip assays, or other methods as determined by SST, Panels and ACC Members)		(Project Development)			

Value to the Chemical Industry

The success metrics of this initiative by the ACC LRI include:

- Demonstration that companies and panels are able to confidently employ these approaches in their product stewardship programs and or regulatory comments or submissions.
- Companies and panels understand potential misapplications of these methods, and thus can document and communicate such misapplications when others use these methods to raise ill-founding allegations of impacts on health or the environment.

IV. Defining Future Success for the LRI Program

The LRI Research Strategy 2020-2024 focuses on research results that can support many regulatory, advocacy and product stewardship needs. Figure 2 identifies areas where the ACC LRI program has been designed to be particularly impactful.

Table 5. Elements for LRI Success

Improved Chemical Safety Assessment	ACC Advocacy and Public Policy	Advances in Communication
Innovations in predictive models for exposure data that can fill existing information gaps and advance assessment of risks from chemicals	Research approaches for addressing the needs of the new TSCA for priority setting, risk-based screening and in-depth risk assessments	Research outcomes that increase public confidence in the products of the chemical industry
Innovations in new approach methods for chemical testing to support company product-defense efforts, new product development, and sustainable design of new materials	Development of scientific confidence in new approach methods that enable sound risk-decisions to be made more rapidly, at lower cost and with fewer lab animal studies	Quality LRI research that advances the credibility of industry science
Approaches for evaluating new chemicals that more rapidly and cost-effectively identify products and processes that meet the safety criteria	Continued research collaborations with EPA and other agencies	Effective communication of research outcomes regarding advances in chemical safety for business executives, the public, and others
Approaches that integrate new technologies and exposure science to enable risk-based prioritization of 20,000 – 30,000 chemicals under TSCA to permit low risk substances to be rapidly de-prioritized	Research approaches that address public demands for more information about product safety	Communication of the scientific basis for reaching risk-based conclusions that substances de-prioritized using advanced computational methods for hazard and exposure are safe for their intended conditions of use

The ACC LRI will continue to enhance its communication efforts to members, stakeholders and the general public to demonstrate the importance and contributions of the ACC LRI. These activities are summarized in Table 6. The hyperlinks are to specific LRI communication materials which illustrate the types of communication work products LRI will develop.

This ACC LRI 2020-2024 Research Strategy has been developed to complement priorities of ACC's programs, particularly those focused on successful implementation of the new

requirements in TSCA. Implementation of the new TSCA has created its own set of anticipated and unanticipated challenges. Focusing LRI research on these challenges over the next 5 years will facilitate generation of more rapid, cost-effective and less animal-intensive data for chemical safety determinations for use in TSCA and product stewardship.

Table 6. LRI Communication Focus Areas 2020-2024

LRI Communication Focus Areas	Web Links
ACC LRI public web site landing page (LRI overview, LRI program web vide, LRI Principles, sliders emphasizing new research, workshops, accomplishments).	https://lri.americanchemistry.com/
ACC Research Catalog (publicly accessible, searchable database of over 850 scientific publications produced by researchers supported by the ACC LRI. More recently, efforts have been launched to include research supported by other ACC programs).	https://lri-researchcatalog.americanchemistry.com/
ACC LRI scientific tools and methods. Specific tools and methods developed through the ACC LRI can be accessed by members, stakeholders and the public. These include methods to investigate and characterize toxicity, exposures, dosimetry, and risks.	https://lri.americanchemistry.com/LRI-Research-Program/Scientific-Tools-and-Methods.html
ACC Science & Research Highlights provide concise research and impact summaries intended for audiences with varying degrees of technical expertise in the topics covered.	https://lri.americanchemistry.com/Science-and-Research-Highlights.html
ACC LRI and ICCA LRI Workshops and Conferences: the ACC LRI and its International Council of Chemical Associations (ICCA) partners organize workshops to foster interactions among researchers and stakeholders, to stimulate discussions that can improve the scientific basis for policy-making and to support consensus building that can advance the risk assessment process. Workshop proceedings/reports and outcomes are communicated to ACC members, stakeholders and the public.	https://lri.americanchemistry.com/LRI/LRI-Workshops/