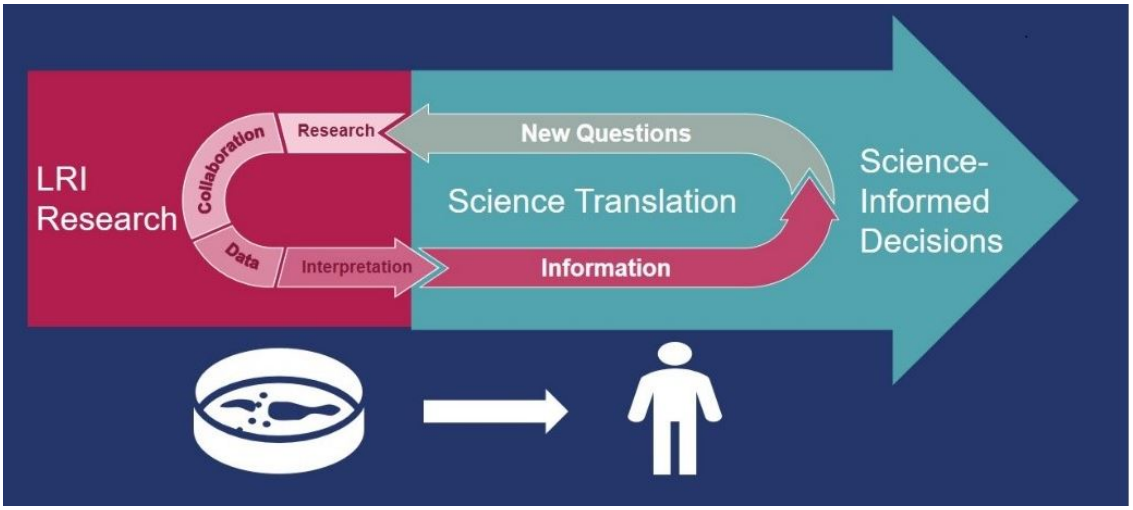
Science Highlight from the ACC LRI | March 31, 2021

Improving Methods to Predict In Vivo Effects from In Vitro Test Systems: Dosimetry Modeling is Key



New Publication

"Predictive modeling of biological responses in the rat liver using *in vitro* Tox21 bioactivity: Benefits from high-throughput toxicokinetics"

- Advanced approaches for evaluating the safety of chemicals envision using a variety of New Approach Methods (NAMs) to profile biological activities of chemicals instead of using traditional laboratory animal toxicity tests to measure toxicity.

  ✓ NAMs are defined as any technology, methodology, approach, or combination that can provide information on chemical hazard and risk assessment to avoid the use of animal testing.

  ✓ TSCA now requires NAMs to be used in lieu of traditional animal toxicity tests when NAMs can provide information of equivalent or better scientific quality. Sufficient scientific confidence in NAMs needs to be established before application in regulatory and product stewardship safety evaluations.

  ✓ In September 2019, EPA 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, one pillar of the LRI Research Strategy 2020-2024 focuses on supporting collaborative research to actualize *in silico*, *in vitro* and tiered testing and assessment approaches that can be used to more efficiently evaluate the safety profiles of chemicals.

- A new research study (Ring et al., 2020, "Predictive modeling of biological responses in the rat liver using *in vitro* Tox21 bioactivity: Benefits from high-throughput toxicokinetics" explored how well *in vitro* data can predict effects observed in laboratory animals.

✓ This study tested the hypothesis that "*in vitro* high-throughput screening data can more effectively predict *in vivo* biological responses when chemical disposition and toxicokinetic (TK) modeling are employed."

✓ The ability of NAMs to predict the effects of chemicals observed in traditional laboratory animal tests is one of the many significant scientific challenges that must be addressed.

✓ Scientists from the University of North Carolina, Texas A & M, NIEHS and ToxStrategies collaborated on this research project. This research was supported, in part, by the ACC Long-Range Research Initiative in association with the Foundation for Chemistry Research and Initiatives.

✓ This new research shows that chemical disposition and toxicokinetics need to be evaluated, both *in vitro* and *in vivo*, to effectively predict *in vivo* biological responses to chemicals from *in vitro* NAMs.

- The nominal concentration — the amount of an ingredient which is expected to be present in an *in vitro* cell-based assay — does not necessarily equate to the actual concentration within the media or cells.
- Using the Armitage model, a method developed previously through ACC LRI support, Ring and colleagues converted effect levels associated with nominal *in vitro* concentrations to effect levels associated with cell media and intracellular concentrations.
- Using EPA's HTTK method, Ring and colleagues also converted *in vivo* hepatic effect concentrations from studies in rats to concentrations in plasma.
- These researchers then applied advanced modeling approaches using machine learning to explore how well *in vitro* responses could predict *in vivo* responses.
- **The "best" models were those that included *in vitro* doses converted to media and intracellular concentrations and *in vivo* doses converted to concentrations in plasma and liver.**
- The "worst" models were those that used *in vitro* nominal concentrations and *in vivo* applied doses.

- **The bottom line: application of knowledge, methods, and models of *in vitro* chemical disposition and *in vivo* toxicokinetics are key to developing better methods to predict *in vivo* biological responses.**

✓ The ACC LRI has been at the forefront in catalyzing research to develop and apply toxicokinteic methods for in vivo and in vitro applications for many years.

- Visit the ACC Research Catalog to explore scientific publications of the research supported by the ACC LRI.
- Visit the Scientific Tools and Methods ACC LRI web page to learn more about specific methods and tools developed to evaluate and characterize toxicity, exposures, dosimetry, and risks by investigators supported by the LRI.

This Science Highlight was prepared by Richard A. Becker Ph.D. DABT of the ACC LRI. The views expressed are his alone.

To learn more about the ACC LRI visit our website https://lri.americanchemistry.com/