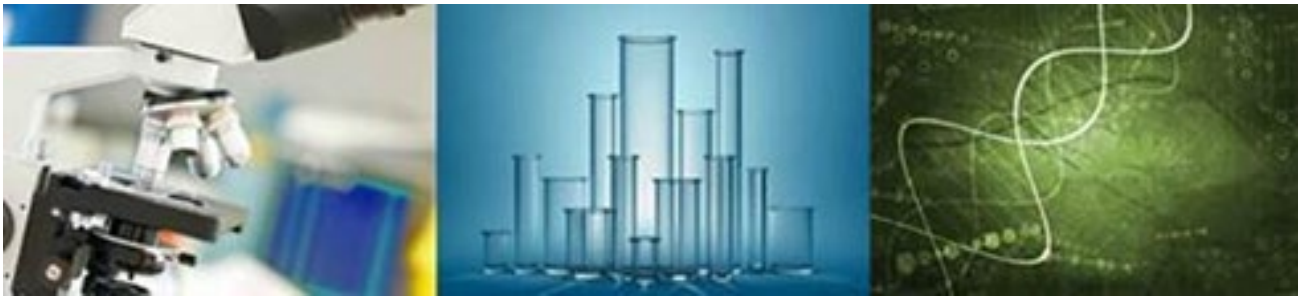


ACC Science & Research Highlights

Developing Context Appropriate Tiered Toxicity Testing Approaches Using New Alternative Methods (NAMs)

February 19, 2020

The LRI-sponsored research presented in the recent open access publication *Developing Context Appropriate Toxicity Testing Approaches Using New Alternative Methods (NAMs)* utilizes 21st century science to incorporate NAMs of differing nature and complexity into a framework for tiered chemical safety testing and risk-based evaluations. **The sections below are adapted excerpts from this publication.**

This tiered framework actualizes a strategy which:

- Integrates bioactivity with exposure at each decision node to support risk-based decision making;
- Incorporates ACC LRI-supported research on computational methods, such as TTC, IVIVE, fit-for-purpose assays, and toxicogenomics; and
- Advances the vision (and statutory requirements) to improve risk-based approaches in TSCA through use of NAMs that can reduce reliance on traditional animal testing methods.

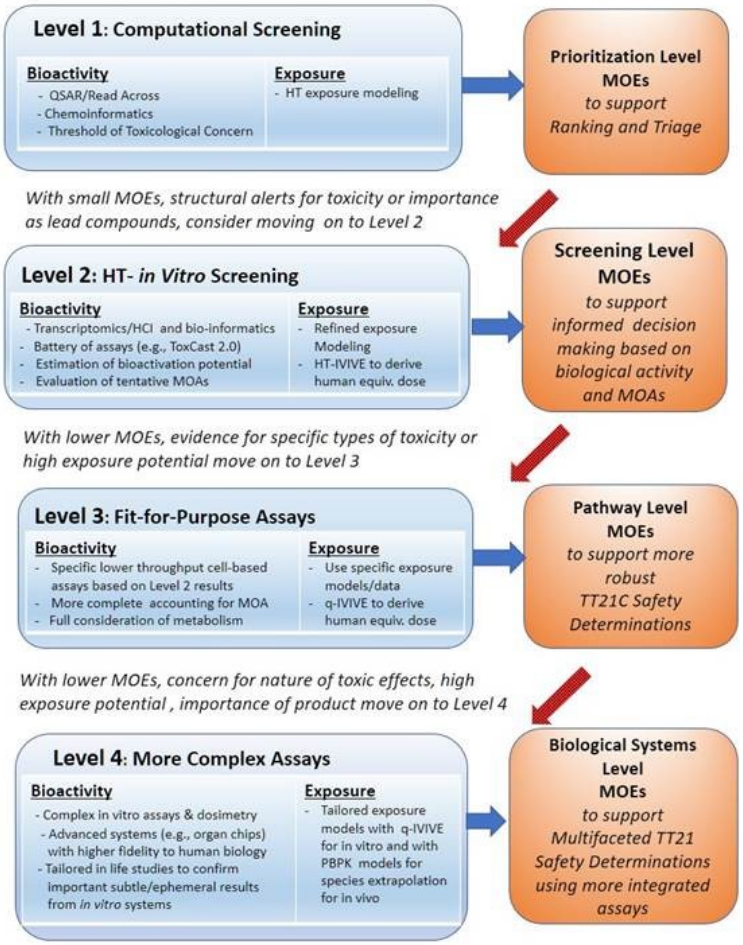
The Tiered Framework

Depicted in Figure 1 below, the framework outlines application scenarios for NAMs in different risk contexts and places different NAMs and conventional testing approaches into four broad levels. Each level also includes decision-appropriate exposure assessment tools.

- Level 1 relies solely on computational screening
- Level 2 consists of high throughput in vitro screening with human cells intended to provide broad coverage of possible responses
- Level 3 focuses on fit-for-purpose assays selected based on presumptive modes of action (MOA) and designed to provide more quantitative estimates of relevant dose responses
- Level 4 includes a variety of more complex multi-dimensional or multi-cellular assays and might include targeted in vivo studies to further define MOA.

This tiered testing and risk-based evaluation strategy is problem formulation-driven. The level of information available about chemicals will guide the particular testing for use conditions. The progression through different levels (orange arrows) is governed by decision context. Depending on the margin-of-exposure (MOE) estimated at each level, a decision-maker might still regard the information at any specific level to be insufficient, leading to consideration of higher level testing to refine the analysis and have a greater degree of confidence in a decision.

Figure 1. A multi-level strategy for using new alternative methods and higher-throughput exposure tools for context dependent safety assessments
(Figure from Andersen et al. (2019) “Developing context appropriate toxicity testing approaches using new alternative methods (NAMs)”, ALTEX - Alternatives to animal experimentation, 36(4), pp. 523-534. doi: 0.14573/altex.1906261.)



Lessons Learned and Path Forward

With the explosion of available NAMs in the past decade and changes in the regulatory environment afforded by various initiatives such as the Frank R. Lautenberg Chemical Safety for the 21st Century legislation, it is necessary to lay out how information developed using NAMs will shape approaches for various risk assessment decisions.

Decision context is the key; there is no one-size-fits-all solution. Importantly, most risk-based decisions should not be viewed as requiring each compound or classes of compounds through a tiered strategy (i.e., going from Level 1 through Level 4).

- Moving through just one or two of these levels should allow decisions about relative risks of products, including absence or low degree of potential anticipated toxicity and low expected exposure (i.e., very high MOSs or MOEs).
- Level 2 and 3 assays should provide the necessary information for assessing MOAs, AC50s or LECs and, when combined with improved human exposure assessment methodologies, are likely to become preferred approaches for most safety assessments.

In addition, the framework can also help to identify where additional scientific research is needed to build greater confidence in various NAMs so that they can be used in the future with the necessary degree of confidence.

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