U.S. National Academy of Sciences Study Update

Variability and Relevance of Current Laboratory Mammalian Toxicity Tests and Expectations for New Approach Methods (NAMs) for use in Human Health Risk Assessment

OECD WPHA Teleconference

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Background

- Relatively few environmental and commercial chemicals have toxicity data in the species of interest (i.e., humans).
- Mammalian *in vivo* laboratory tests are currently used as models for human toxicity and are a part of the foundation of the current chemical risk assessment paradigm.
- Language in amended TSCA requires alternatives or New Approach Methods (NAMs) to provide “information of equivalent or better scientific quality and relevance…” than the traditional mammalian *in vivo* toxicity tests, and TSCA as well as other statutes include statements on using “the best available science”.
- The traditional approach to validating NAMs frequently requires a time and resource intensive ring trial and a one-for-one comparison with an endpoint(s) from a mammalian *in vivo* toxicity test, where this type of comparison may not be applicable for every NAM.
- Previous NAS committees have recognized that there are challenges in validating NAMs when limited data exists on the species of interest (i.e., humans).

EPA United States Environmental Protection Agency

Reasons for the Study

- NAMs are frequently held to a different standard than traditional mammalian toxicity tests.
- The variability of mammalian *in vivo* toxicity studies has not been fully characterized.
- Many of the mammalian *in vivo* toxicity studies have not been validated in the traditional context relative to human responses.
- The endpoints for some mammalian *in vivo* toxicity studies have shown limited concordance to human responses.
- A one-for-one replacement approach is not applicable to all regulatory decisions.
- Different regulatory decision contexts necessitate different approaches to validation and levels of confidence.

Committee Statement of Task

The National Research Council (NRC) will perform a comprehensive literature review on the variability and human relevance of current laboratory mammalian toxicity tests as well as approaches to validation and establishing scientific confidence in using NAMs. The variability and relevance of the existing laboratory mammalian toxicity tests shall be considered by the NRC in terms of reliability, qualitative and quantitative reproducibility as well as biological relevance and overall concordance of the results in humans. The NRC will convene a committee to synthesize and interpret the results from the literature review and provide recommendations for consideration related to the following:

- Variability of laboratory mammalian toxicity tests and concordance with human adverse responses.
- How the variability in traditional mammalian toxicity test results and concordance with adverse effects in humans can be used to inform benchmarks in evaluating the scientific quality of NAMs.
- Key components that should be considered in a fit-for-purpose validation paradigm or scientific confidence framework for NAMs where there is no existing standard test, the standard test is not relevant to the human response, or the standard test has not been benchmarked against human responses.

Types of Recommendations Requested

Literature Review

- The range of qualitative and quantitative variability in traditional mammalian toxicity test results.
- The concordance of laboratory mammalian toxicity tests with adverse effects in humans and endpoints with higher and lower concordance.

Committee Recommendations

- How the variability in traditional mammalian toxicity test results and concordance with adverse effects in humans can be used to inform expectations in evaluating the scientific quality of NAMs.
- Key components that should be considered in a fit-for-purpose validation paradigm or scientific confidence framework for NAMs where there is no existing standard test, the standard test is not relevant to the human response, or the standard test has not been benchmarked against human responses.

Committee Members

Weihsueh A. Chiu – Texas A&M University (Chair)

Kim Boekelheide – Brown University

Patience Browne - OECD

Holly Davies - Washington State Department of Health

Corie A. Ellison – Proctor & Gamble

Marie C. Fortin – Jazz Pharmaceuticals

Nicole C. Kleinstreuer – NICEATM/NTP

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Heather B. Patisaul – North Carolina State University

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Martyn T. Smith – University of California, Berkeley

Robyn L. Tanguay – Oregon State University

Christopher Vulpe – University of Florida

Tracey J. Woodruff – University of California, San Francisco

Joseph C. Wu – Stanford University

Committee Schedule

- Kick off Meeting: September 2021
- First Information Gathering Workshop: December 2021
- Second Information Gathering Workshop: TBD
- Consensus Report: TBD (no later than March 2023)

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Questions