

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

Background for first (virtual) meeting of  
the provisional NAS committee

September 23, 2021

# Disclaimer

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.

# 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 where there is no “gold standard” or against toxicity tests that have not themselves been validated.

# 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.

# 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.

# Expectations

- Use the results of the literature review as the starting point for recommendations.
- Remain focused on evaluating the variability and relevance of the traditional *in vivo* mammalian toxicity testing models and not the variability and relevance of the NAMs.
- The committee is not being asked to provide recommendations on the more general components of a validation and scientific confidence framework as these have been covered by previous NAS and OECD committees.
- Provide recommendations on difficult validation questions that previous NAS committees have not tackled (e.g., what to do when 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).
- Understand there are a broad range of regulatory decisions and that a 'one-size-fits-all' approach to validation or establishing scientific confidence will not meet EPA's needs.

# Types of Recommendations That Will Be Useful

## 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.

**Thank You For Your Service!**