NRC Report: Application of Modern Toxicology Approaches for Predicting Acute Toxicity for Chemical Defense

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Predictive Toxicology Committee

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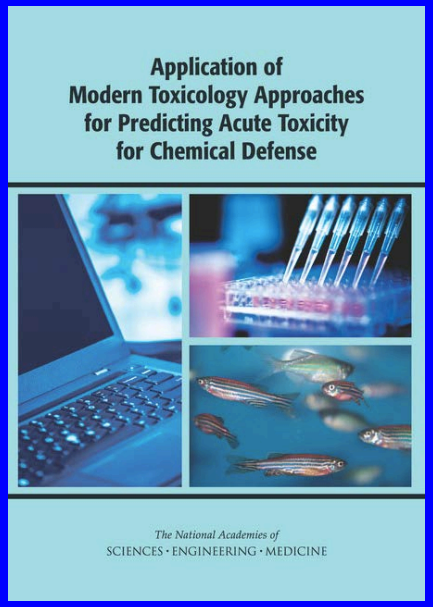
Predictive Toxicology Statement of Task

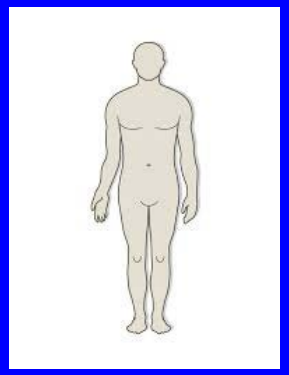
- Consider modern approaches for predicting toxicity and suggest an overall conceptual approach for using such information to predict acute toxicity.
- *This study was not a comprehensive review of current initiatives to develop predictive toxicology programs.*
- *Sponsor: US Department of Defense*



- Report Structure
  - Summary
  - Introduction
  - Conceptual Framework and Prioritization Strategy
  - Nontesting Approaches Relevant to Prediction of Acute Toxicity and Potency
  - Assays for Predicting Acute Toxicity
  - Integration and Decision-Making for Predictive Toxicology
  - Lessons Learned and Next Steps

Traditional Approach

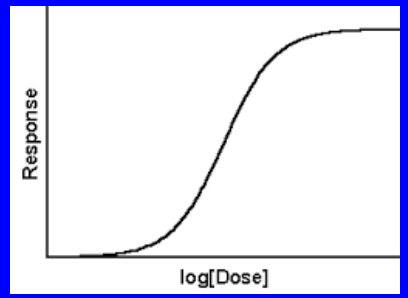
Chemical



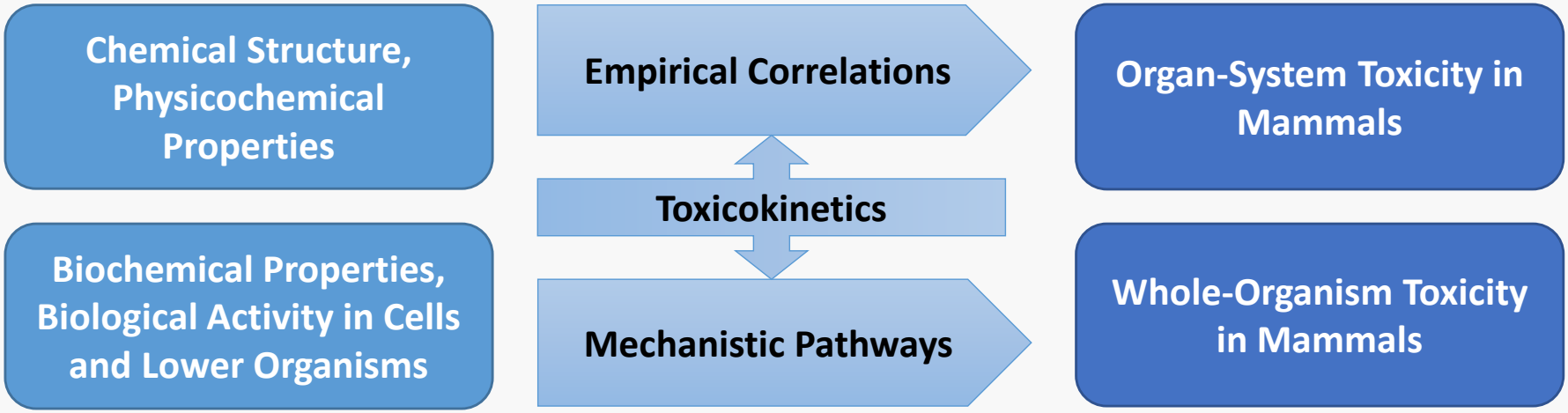
Human

Characterize toxicity (LD_{50}) & organ systems

Animal



CONCEPTUAL FRAMEWORK



The committee's conceptual framework is based on the premise that whole-animal toxicity can be predicted by using information about lower levels of complexity, even down to the level of chemical structure.

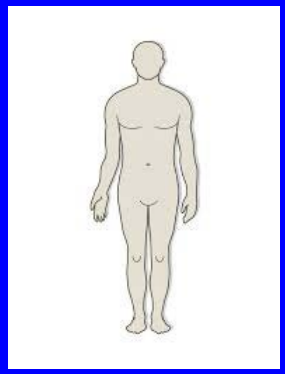
Conceptual Framework

Chemical

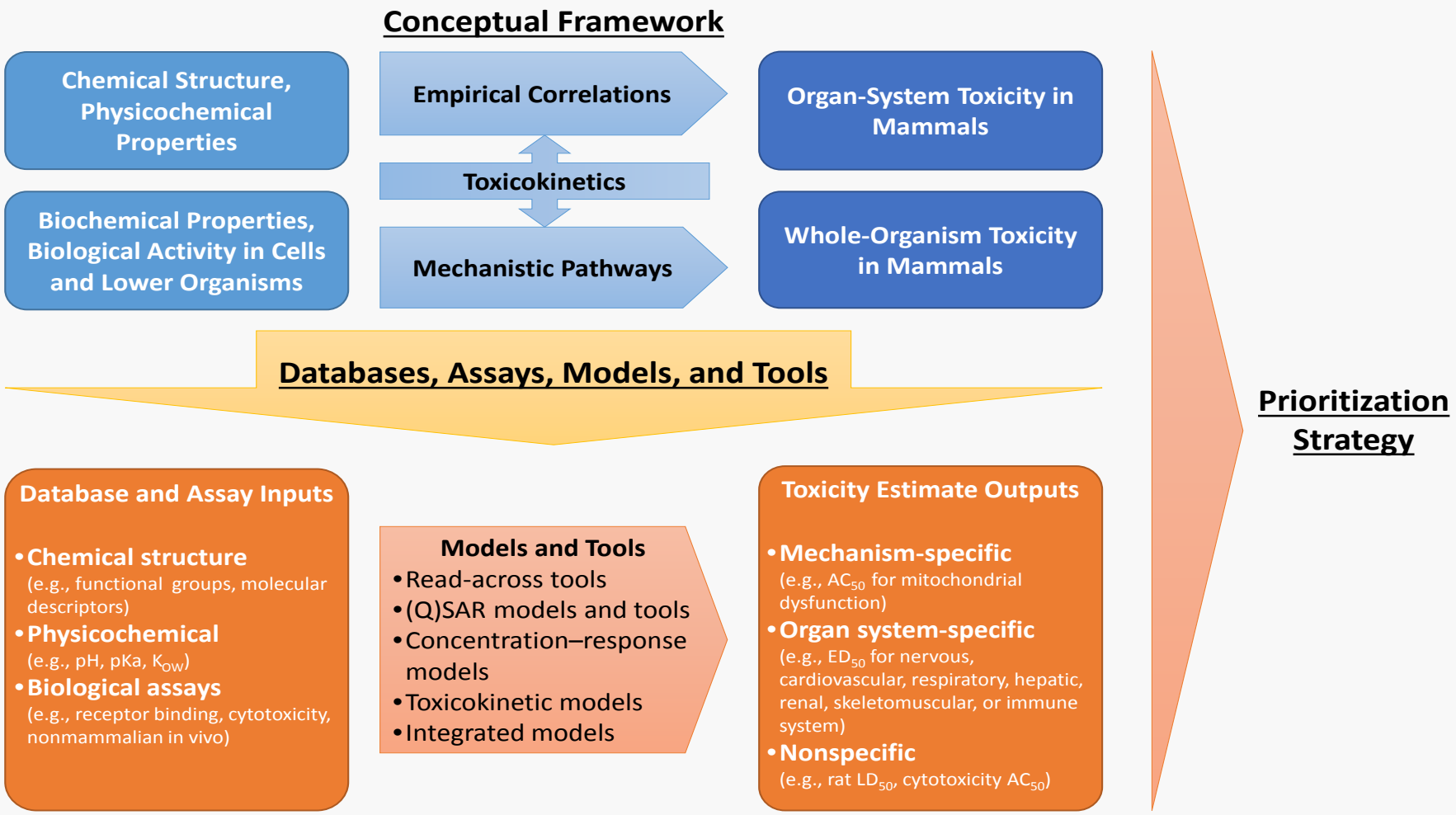
In vitro

In silico

In vivo

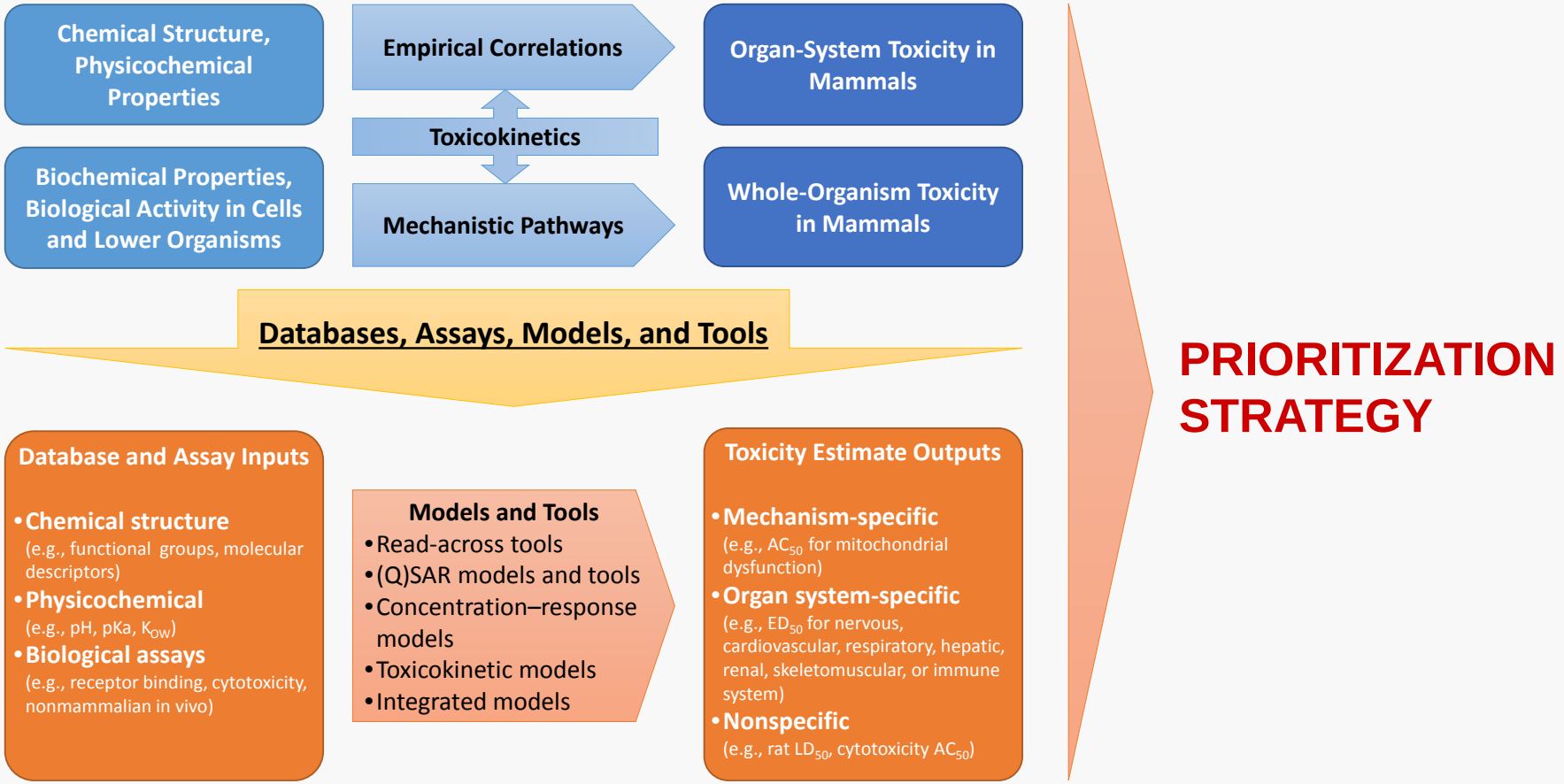


Human



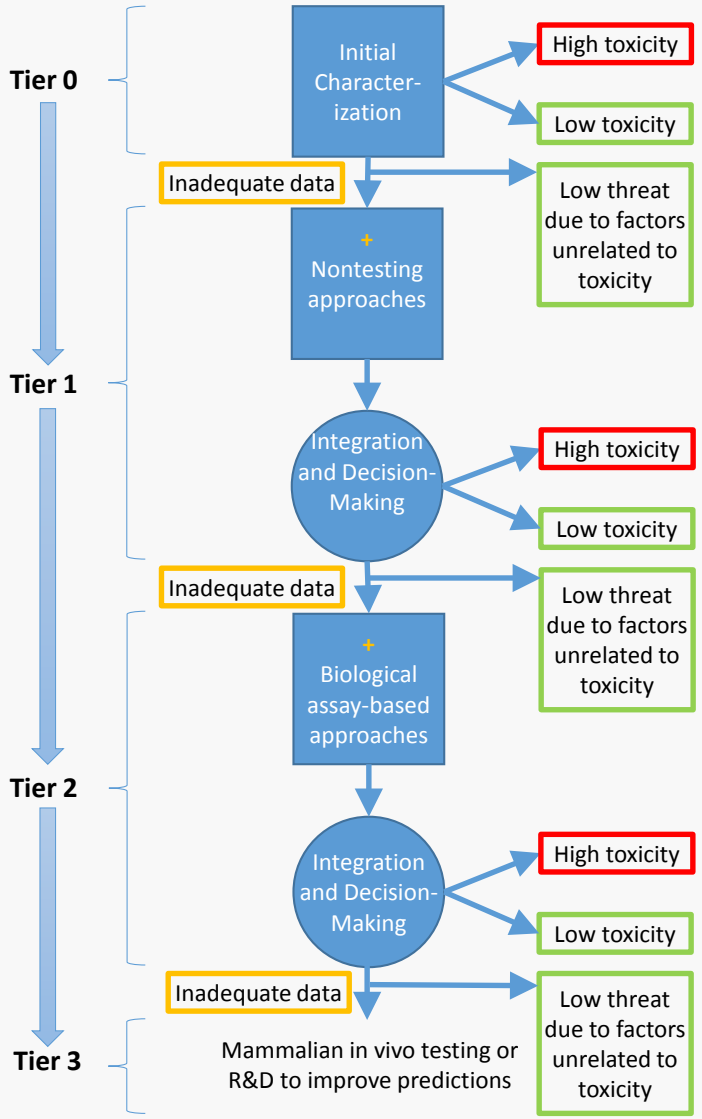
DATABASES, ASSAYS, & TOOLS

CONCEPTUAL FRAMEWORK



DATABASES, ASSAYS, & TOOLS

Prioritization Strategy

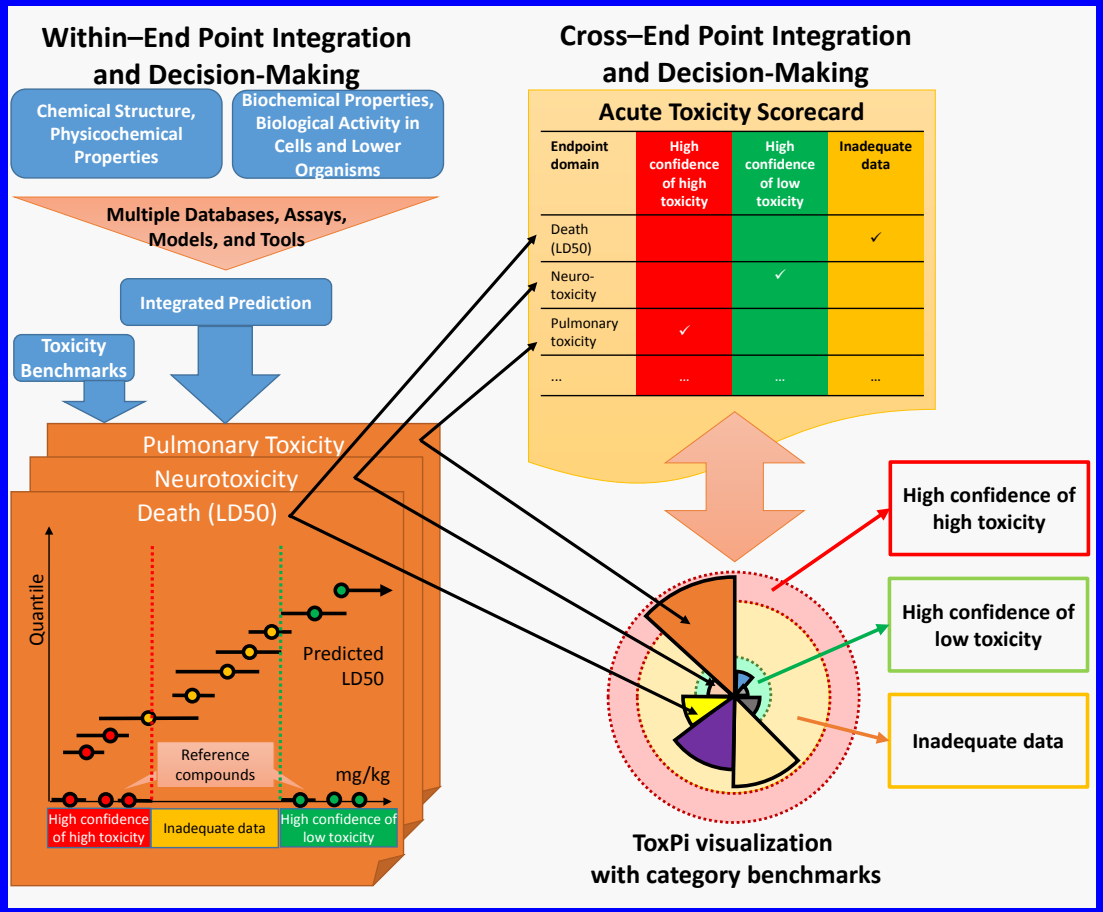


Emphasis on high confidence indicates a low tolerance for false negatives

Chemicals could be deselected at any stage by considering factors other than toxicity.

Progression through the tiers requires intermediate integration steps.

General Approach to Decision-Making



- Define the most informative end points for its purpose (for example, neurotoxicity vs seizures).
- Set boundaries or toxicity thresholds for what is considered "high" or "low" toxicity for each end point.
- Specify the level of confidence needed to make determinations.

Overall Conclusion

The state of the science suggests that development of a predictive acute-toxicity program will require extensive DOD investment in computational modeling approaches, assay development, methods for extrapolation of in vitro results to in vivo conditions, and data-integration methods.

Overall Recommendation

- DOD should initiate pilot studies that evaluate chemical classes of highest concern with well-characterized reference chemicals.
- Pilot studies would allow DOD to accomplish the following:
  - Develop the novel assays and tools needed to predict acute chemical toxicity efficiently and accurately.
  - Evaluate the rate of false negatives and false positives.
  - Examine how generalizable the results of various assays and tools are from one chemical class to another.
  - Begin to address the size of the chemical space needed to make predictions about unknown chemicals.

The committee emphasizes that DOD could benefit from leveraging its efforts with other federal activities, such as EPA's ToxCast program. Such collaboration would allow DOD to complete pilot studies more rapidly and maximize the return on its investment.