National Institute of Environmental Health Sciences
Division of Translational Toxicology

Opportunities for Encouraging the Consideration of Alternative Methods

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Introduction

- Currently, there is little incentive for investigators who have long used specific in vivo models and well-established protocols to work toward adopting new approach methodologies (NAMs).
- Moving to NAMs could provide an opportunity to improve established methods of conducting toxicology testing and research. However, incentives are needed to encourage investigators to actively seek out, validate, or research NAMs.
- The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) established its Consideration of Alternative Methods Workgroup (CAMWG) to explore opportunities to encourage scientists to pursue NAMs that could replace, reduce, or refine their use of live animals.
- Between May 2022 and May 2023, the CAMWG held a series of informational meetings with representatives from different stakeholder groups to document their perspectives on the consideration and use of NAMs in their respective organizations.

CAMWG Scope

- Work with stakeholders to develop a catalog of incentives that could be used to encourage proposals for NAMs in conjunction with existing in vivo test methods.
- Review current requirements for the consideration of NAMs, and how those might be modified or expanded upon to foster additional consideration by stakeholders.
- Consider how these efforts could be broadened beyond toxicology testing to other area of testing and research that involve animal use.

CAMWG Charges

- Work with stakeholders to publish a white paper on ways to encourage the use of NAMs.
- Foster collaborations with authorities outside the U.S. to share ideas and progress to promote greater harmonization for considering NAMs.
- Refer the community to available grants devoted to the development of alternatives to live animal use.
- Identify and improve communication efforts and opportunities that help promote the use of NAMs.
- Encourage agencies to promote avenues where NAMs can be better considered and leveraged.

CAMWG Roster

U.S. Consumer Product Safety Commission	John Gordon
U.S. Department of Agriculture	Jessie Carder (co-chair) Patrice Klein
U.S. Department of Defense	Shannon Marko (co-chair) Alexander Miller
Veterans Health Administration *Office of Research and Development*	Holly Krull
U.S. Environmental Protection Agency (EPA) *Office of Pollution Prevention and Toxics*	Iris Camacho
EPA Office of Research and Development	Alison Harrill
U.S. Food and Drug Administration (FDA) *Center for Drug Evaluation and Research*	Nakissa Sadrieh
FDA Center for Food Safety and Applied Nutrition	Suzanne Fitzpatrick
National Cancer Institute	Brian Cholewa Ron Johnson
National Institute of Environmental Health Sciences	Warren Casey Dori Germolec Helena Hogberg-Durdock Nicole Kleinstreuer
National Institutes of Health	Nicolette Petervary
U.S. National Coordinator for the OECD Test Guidelines Programme	Charles Kovatch
Inotiv, contractor supporting NICEATM *NICEATM Support Staff*	Dave Allen Amber Daniel Oluwakemi Oytetade

Stakeholder Groups

- **Consumer Products**
- **(Bio)Pharmaceuticals**
- **Agrochemicals**
- **University Researchers**
- **IACUC representatives**

Stakeholder Discussion Questions

1. Barriers to implementing NAMs?
2. Suggestions to overcome those barriers?
3. Areas to use NAMs that are currently unavailable?
4. Areas where NAMs are used but are inappropriate?
5. Funding opportunities to research/validate NAMs?
6. Does your group consider or employ the use of NAMs?
7. Methods to prescreen drug or substance candidates for development? Examples?
8. Thoughts on the availability of NAMs (in academia, pharma, etc.)?
9. Thoughts on the current state of NAMs in toxicology testing?
10. Examples of successfully using an alternative approach?
11. Suggestions on communication efforts that would promote the use of NAMs?

How NAMs Are Being Used

Academia Application

- Mechanistic research e.g., organ-on-chips, in vitro models, small model organisms, microphysiological systems, microfluidic devices.
- Basic sciences questions and studies.
- Complementary to whole animal studies.

IACUC Application

- Justification in animal protocols on why an alternative cannot be used.
- Conducting a literature search on alternatives is required for protocol approval.

Industrial Application

- Early screening during chemical or drug development (e.g., leachable/extractables and drug impurity testing, mixtures/formulations studies).
- Internal decision making; product safety testing/risk assessment and hazard characterization (e.g., defining exposure banding/limits).
- Supporting data that are used in a regulatory submission or safety assessment (weight of evidence).
- Complete replacement of an animal study (e.g., used to justify waivers in a regulatory submission)
- Examples include in silico, read across, toxicokinetic (PBPK), ex vivo and in vitro models for eye and skin irritation tests, skin sensitization, and dermal penetration.

Common Themes – Barriers to using NAMs and Solutions

	Barriers	Solutions
Perception	• Hesitancy of stakeholders to use NAMs due to concerns over regulatory acceptance. • Resistance to adopt NAMs by scientists using traditional in vivo approaches. • Misunderstanding that NAMs should map directly to an observable/existing endpoint. • High uncertainty levels with NAMs for complex endpoints.	• Scientists need assurance that NAMs can complement their ongoing work. • Developers and users of NAMs need to be transparent about “fit for purpose” and their limitations. • Established, high-profile scientists can challenge previously published literature that use traditional in vivo models.
Education	• Lack of knowledge on NAMs. • Lack of training and limited time if training was available. • Challenge to find relevant information on NAMs in the literature if not trained on how to properly conduct a literature search in bibliographic databases.	• Need increased awareness on NAMs (e.g., articles, seminars/conferences, case examples, and guidance documents). • Training resources that target non-NAM users (e.g., young scientists and IACUC members). • Communicating to federal/funding agencies benefits of NAMs to their research portfolio.
Scientific/ Technical	• Lack of high-quality reference data. • Technology of NAMs is difficult to transfer to new labs and staff. • Lack of robust NAMs for specific endpoints (respiratory sensitization, developmental reproduction). • Applicability to mixtures/formulations (e.g., polymers, volatiles). • NAM data and results are inconsistent and hard to interpret.	• Clear context of use for validation • Collaboration between industries, contract research organizations, regulatory agencies, and IACUC. • Development of cheaper and simpler alternatives/NAMs are needed. • Animal data should not be relied on as the gold standard.
Regulatory Acceptance	• Lack of harmonization in NAM acceptance criteria. • Inconsistency of acceptance and the extent to which they need to have been formally validated prior to use. • Clarify regulatory information needs and expectations. • Nonexistent/unspecific framework for NAMs.	• Need for state, national and global harmonization of acceptance criteria. • Need to rethink validation and adoption process. • Regulators need to advise NAM developers and users what test methods /NAMs to prioritize. • Need an efficient framework to establish confidence in NAMs.
Funding	• Limited funding available for NAM development. • NAMs are expensive and risks of failure are costly. • High cost to entry (i.e., commercially availability) for some models and platforms.	• Need to identify government and NGO funding sources and make them widely known/publicly available. • Allocate additional funding (e.g., supplements to include refinement approaches and NAMs to existing in vivo funding).

Conclusions and Next Steps

- In general, NAMs are available and used by various stakeholders.
- There are areas and application domains where NAMs are not yet suitable, while some areas have ample supply of NAMs (e.g., skin irritation/corrosion).
- More dialogue is needed on priorities and needs between regulators and NAMs developer and end-users.
- Those not using NAMs need targeted support and education on using NAMs to non-NAMs users.
- Increased funding will develop and incorporate NAMs in research and regulatory applications.
- The CAMWG aims to publish a white paper with stakeholder responses and recommend implementation for some of the solutions.

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