Reviewing the Method Developers Forum –

Follow-on activities from the VWG Report

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INOTIV-RTP, CONTRACTOR SUPPORTING NICEATM

Background

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (**NICEATM**) provides technical and scientific support for the Interagency Coordinating Committee for the Validation of Alternative Methods (**ICCVAM**).

ICCVAM Authorization Act of 2000: To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new and revised toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing (**3Rs**) animal tests and ensuring human safety and product effectiveness.

Regulatory Agencies

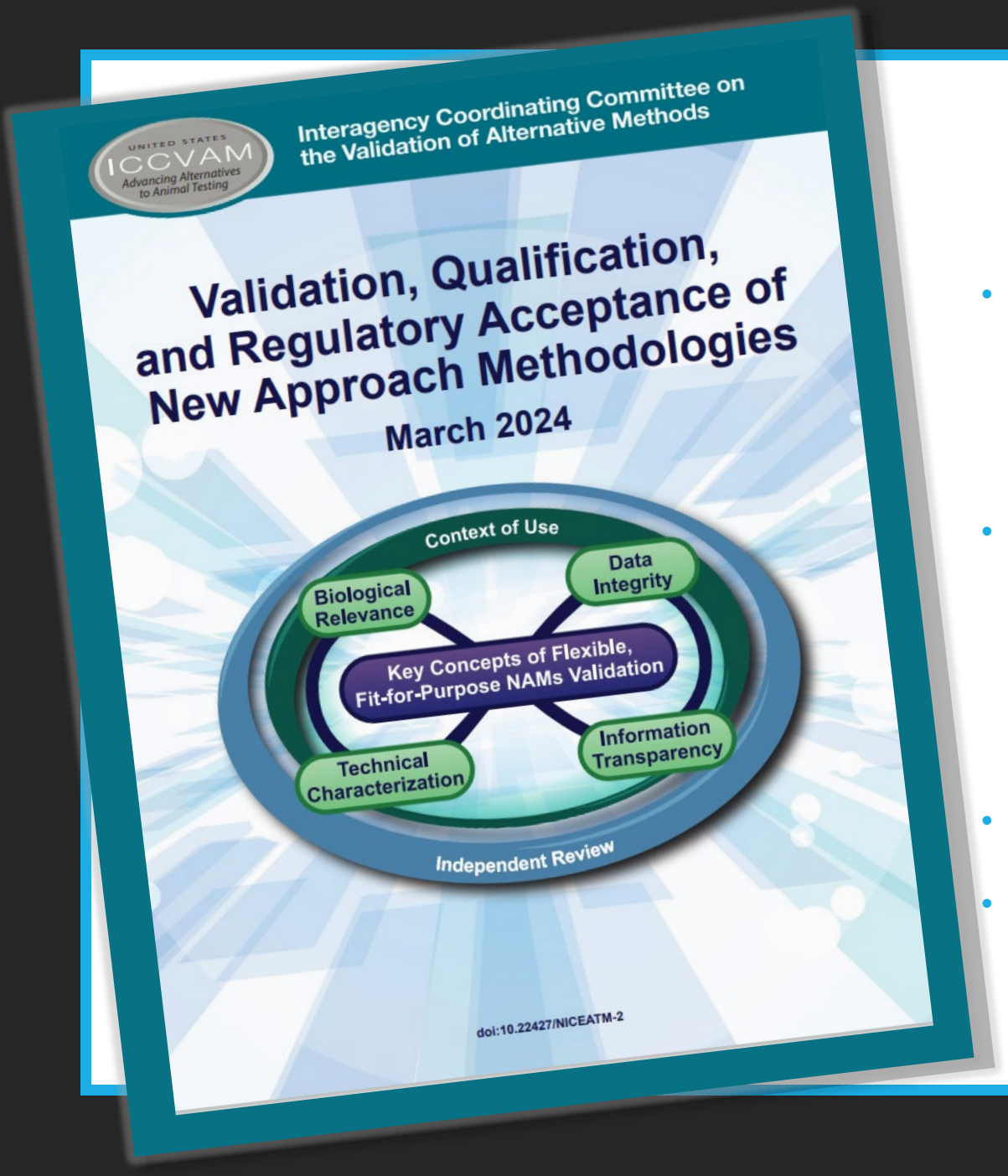
Consumer Product Safety Commission
Department of Agriculture
Department of the Interior
Department of Transportation
Environmental Protection Agency
Food and Drug Administration
Occupational Safety and Health Administration

Research Agencies

Agency for Toxic Substances and Disease Registry
National Institute for Occupational Safety and Health
National Cancer Institute
National Institute of Environmental Health Sciences
National Center for Advancing Translational Sciences
National Library of Medicine
National Institutes of Health
Department of Defense
Department of Energy
National Institute of Standards and Technology
Veterans Affairs Office of Research and Development

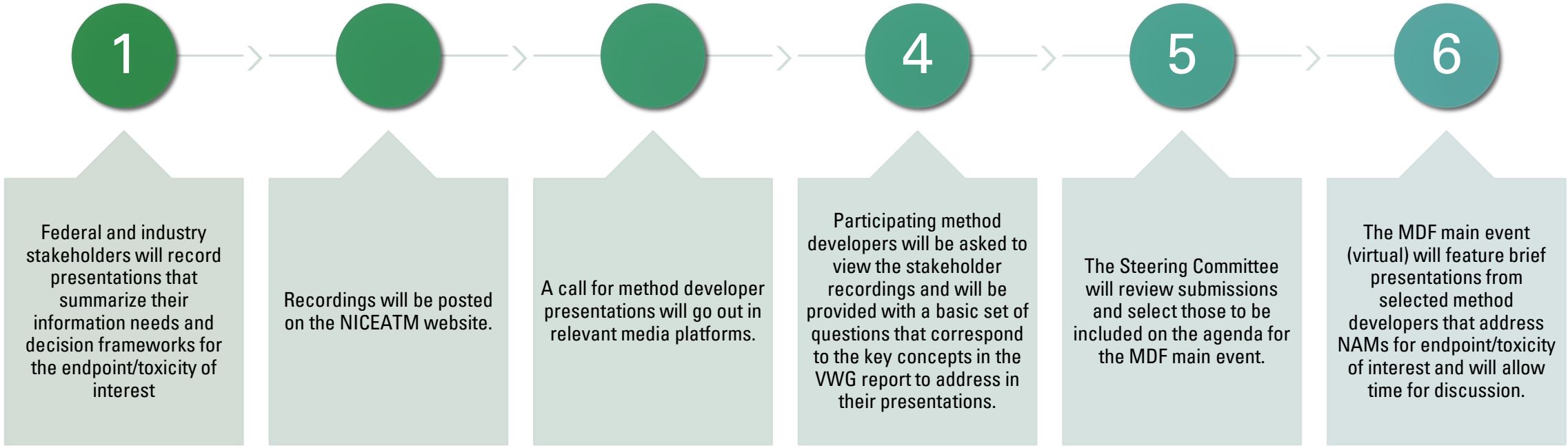
Other participants include Tox21 Representatives.

More information:
https://ntp.niehs.nih.gov/go/iccvam



- March 2024: ICCVAM Validation Workgroup (VWG) published a report on Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies (NAMs).
- The Method Developers Forum (MDF) series is a proactive effort to highlight and implement the recommendations detailed within the VWG report. It provides an opportunity for NAMs developers to present their methods and discuss regulatory issues with relevant stakeholders.
- ICCVAM anticipates holding ~3 MDFs per year.
- Each iteration will focus on a specific endpoint/toxicity.

MDF Process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Federal and industry stakeholders will record presentations that summarize their information needs and decision frameworks for the endpoint/toxicity of interest
Recordings will be posted on the NICEATM website.
A call for method developer presentations will go out in relevant media platforms.
Participating method developers will be asked to view the stakeholder recordings and will be provided with a basic set of questions that correspond to the key concepts in the VWG report to address in their presentations.
The Steering Committee will review submissions and select those to be included on the agenda for the MDF main event.
The MDF main event (virtual) will feature brief presentations from selected method developers that address NAMs for endpoint/toxicity of interest and will allow time for discussion.

First MDF Topic: NAMS for Carcinogenicity Testing

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Federal and industry stakeholders will record presentations that summarize their information needs and decision frameworks for carcinogenicity.

Sector	Speaker	Affiliation
U.S. Federal	John Gordon	CPSC
	Sarah Dobreniecki	EPA/OPP Health Effects
	Keith Salazar	EPA/OPPT New Chemicals
	Sabine Francke	FDA/CFSAN
	Paul Brown	FDA/CDER
	Brian Cholewa	NCI
	Todd Stueckle	NIOSH
	Janet Carter	OSHA
Agrochemicals	Alex Charlton	Syngenta
Case Study	Carole Yauk	Univ. of Ottawa

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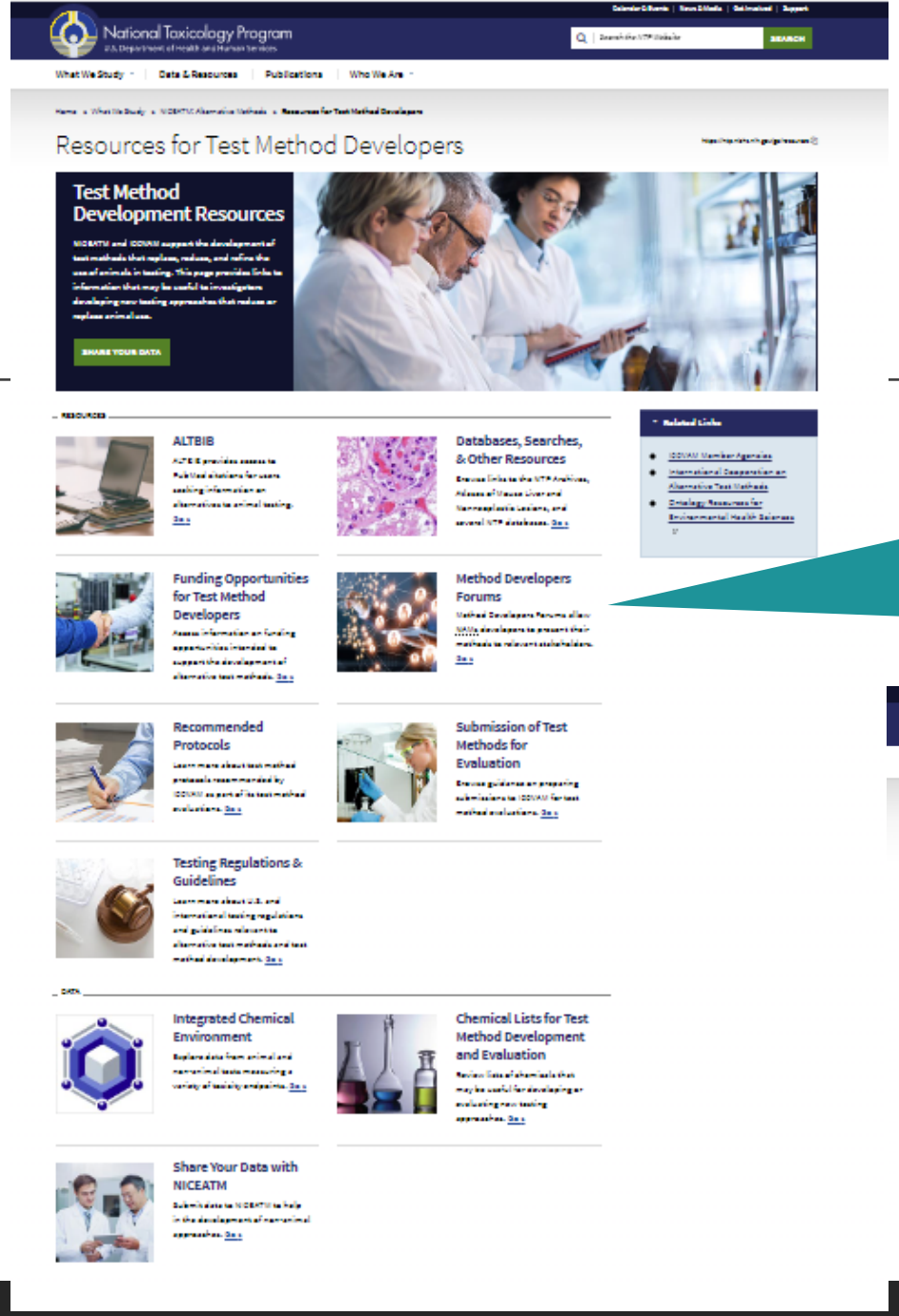
Recordings will be posted on the NICEATM website.



A new child page dedicated to MDF includes stakeholder recordings, instructions for submitting a method, and deadlines.

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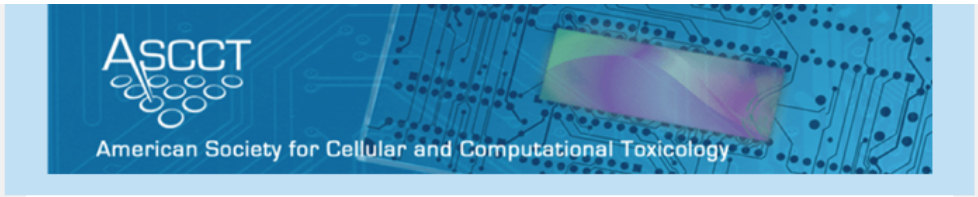
A call for method developer presentations will go out in relevant media platforms.

NICEATM News

- Workshop on Probabilistic Methods for Health Assessments October 7-8
- ICCVAM Method Developers Forum on NAMs for Carcinogenicity Testing: Deadline for proposals extended to August 9
- New ALTBIB topic-specific searches
- Slides and video available for ICCVAM Public Forum
- More NICEATM news items
- Strategic Roadmap
- **Subscribe to NICEATM News email list**



Dear Emily,

ICCVAM Requests Proposals of NAMs for Carcinogenicity

Submission Deadline: July 26, 2024

As a follow-up to the publication of the report on **Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies**, ICCVAM and NICEATM will create a platform for highlighting the report's recommendations by organizing a series of Method Developers' Forums (MDFs), each focused on a specific endpoint/toxicity, that provide an opportunity for NAMs developers to discuss their methods and regulatory issues with relevant stakeholders.

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Participating method developers will be asked to view the stakeholder recordings and will be provided with a basic set of questions that correspond to the key concepts in the VWG report to address in their presentations.

Method Description

Provide a brief overview of your method and its relevance to carcinogenicity testing.

a. Be sure to include enough technical detail and data for regulatory and industry stakeholders to understand how your method may meet their needs. Consider that your audience will potentially include both people who will be running the assay in the lab and people who will only be interacting with and interpreting the assay data and outcomes.

b. Describe any limitations of the applicability domain (e.g., types of chemicals that cannot be tested using the method, types of chemicals for which the results produced by that method are considered unacceptable).

Context of Use

Context of use refers to a clearly articulated description delineating the manner and purpose of use for a particular method, approach, or application. Establishing context of use includes crafting a statement that fully and clearly describes the way a method is intended to be used and its regulatory purpose (if applicable). Using the following questions as a guide, describe your method's specific context of use and the regulatory testing need(s) it addresses.

a. How is your method intended to be used (e.g., chemical screening, hazard identification, potency evaluation, developing adverse outcome pathways (AOPs), point of departure, identification for qualitative or quantitative risk assessment)?

b. What regulatory testing need does your method address (e.g., replacing an animal assay, investigating mode of action or therapeutic target, or targeted endpoint of evaluation)?

c. What regulatory space does your method address (e.g., agrochemicals, pharmaceuticals, medical devices, cosmetics, food/food additives, industrial chemicals)?

d. Has data generated by your method been used for regulatory submissions?

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Participating method developers will be asked to view the stakeholder recordings and will be provided with a basic set of questions that correspond to the key concepts in the VWG report to address in their presentations.

Biological Relevance

Biological relevance refers to a measure of appropriateness for assessing the effects of a chemical within the taxa of interest. Using the following questions as a guide, describe the relationship between your method and the carcinogenesis process.

a. Mechanistic understanding: How does the information provided by your method support known mechanistic knowledge of the carcinogenesis process (e.g., an AOP or toxicologically relevant biological process)?

b. Reference compounds: What are well-characterized and understood compounds that can be used or were used to assess the scientific validity or transferability of your method?

c. Comparison to existing laboratory animal methods: How does your method provide information that is equivalent or better than that from existing methods used for regulatory purposes? How does your method contribute to the reduction, refinement, or replacement of animal assays, and what complementary method development might be needed to comprehensively address carcinogenesis?

Technical Characterization

Technical characterization is a key aspect to demonstrating the quality and scientific validity of a method. Using the following questions as a guide, describe how your method has been characterized.

a. How have the sources of variability (e.g., interference, culture conditions, technique, contaminants) been evaluated?

b. How has robustness (i.e., the ability of the method to be reproduced under different conditions or circumstances, withoutthe occurrence of unexpected differences in the obtained results) been evaluated?

c. How has intra-laboratory reproducibility (i.e., the consistency of individual test results obtained within a laboratory using the same test protocol and test samples) been evaluated? d. How has transferability (i.e., the ability of the method to be accurately and reliably performed in different, competent laboratories) been evaluated (if relevant)?

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The Steering Committee will review submissions and select those to be included on the agenda for the MDF main event.

Of submissions received; topics included:

- Error corrected sequencing for clonal expansion
- Genotoxicity and mode of action
- Whole genome transcriptomic method for carcinogenicity testing
- Cell proliferation and clonal expansion of cancer driver mutants
- Next generation/human relevant carcinogenicity assessments
- Reporting framework to support a weight of evidence safety assessment without long-term rodent bioassays
- Assay panel for test agent prioritization
- Mode of action approach to cancer safety assessments

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The MDF main event (virtual) will feature brief presentations from selected method developers that address NAMs for carcinogenicity and will allow time for discussion.

Featured Presentations

The Chicken Egg Model: An Alternative Model for Detection of Genotoxic Carcinogens
Tetyana Cheairs, Department of Pathology, Microbiology and Immunology, New York Medical College

ToxTracker Discussion: A Potential New Approach Method for Carcinogenicity Testing
Dan Roberts, Toxys, Inc.

Validation of Cell Proliferation as a Key Event in the Assessment of Non-Genotoxic Carcinogenicity
Christian Strupp, Gowan Crop Protection Ltd.
Miriam Jacobs, UK Health Security Agency

Clonal Expansion of Cancer Driver Mutants by CarcSeq: A Biomarker of Carcinogenicity
Barbara Parsons, US Food and Drug Administration National Center for Toxicological Research

Human Relevant Genetic Toxicology for Risk Assessment
Leslie Recio, ScitoVation
Jamie Scaglione, ScitoVation

BioMAP® Assay Panel for Test Agent Prioritization: Support for Carcinogenicity-related Assessments
Ellen Berg, Alto Predict, LLC

ReCAAP: A Reporting Framework to Support a Weight of Evidence Safety Assessment Without Long-term Rodent Bioassays
Gina Hilton, PETA Science Consortium International
Amber Goetz, Syngenta Crop Protection, LLC

γH2AX/pH3 Method for Genotoxicity Mode of Action Determination
Marc Audebert, UMR1331 ToxAlim, French National Institute for Agriculture, Food, and Environment (INRAE)

A Platform for Next Generation Carcinogenicity Assessments
Chris Barber, Lhasa Limited
Adrian Fowkes, Lhasa Limited

Error Corrected Sequencing for Clonal Expansion
Connie Mitchell, Health and Environmental Sciences Institute (HESI)
Jesse Salk, Green Umber, LLC

MDF Main Event

- Wednesday, August 21 and Thursday, August 22 at 9am-12pm Eastern
- Total Presentations: 10
- Total Attendees
  - Wednesday: 194
  - Thursday: 141
  - Over both days ~230 unique
- Both sessions were recorded and posted to the NICEATM MDF website

Primary Outcomes from MDF

Lessons Learned

- Building appropriate timelines in for obtaining Federal Agency presentations (clearance)
- Increase engagement from industry, pre-regulated space
- Provide more opportunities for followup and discussion (in the forum and afterwards)
  - Both directions between Method Developers and End users (industry and regulatory)
- Find ways to prioritize methods that are closer to “ready”
- Providing clear evaluation criteria for method developers to follow in developing their proposals is crucial and helps the steering committee come to a consensus on acceptance

Extremely well received, with positive feedback from diverse stakeholders

Future Plans

Select next topic

- Cardiovascular toxicity
- Inhalation toxicity
- Developmental and Reproductive toxicity
- Specific target organ toxicity (e.g., liver)
- Neurotoxicity
- Systemic toxicity

Gather Federal Regulatory agency input on above topics to be “queued up” for future MDFs

Expand to other regions

- Use template for ICATM partners to have similar events for their regulatory agencies
- Harmonization/coordination into OECD pipeline
- WC13 session?

Acknowledgments

MDF Steering Committee

• **John Gordon** (CPSC) • **Natalia Vinas** (DoD) • **Anna Lowit** (EPA/OPPT)

Renee Beardslee (EPA/OPPT) • **Paul Brown** (FDA/CDER) • **Suzy Fitzpatrick** (FDA/CFSAN)

Warren Casey (NIEHS) • **David Crizer** (NIEHS) • **Steve Ferguson** (NIEHS)

Nicole Kleinstreuer (NIEHS/NICEATM) • **John Elliott** (NIST) • **Elijah Petersen** (NIST)

• **Kelly Magurany** (NSF International)

NICEATM Support

Todd Auman • Amber Daniel

Emily Reinke • Cathy Sprankle

Steven Morefield

NIEHS A/V Support

Parris Milly • Nathan Mitchiner

Chris Schnur • John Maruca