ICCVAM Validation Workgroup Report

Elijah Petersen, NIST

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture • Department of Defense
Department of Energy • Department of the Interior • Department of Transportation • Department of Veterans Affairs Office of Research and Development
Environmental Protection Agency • Food and Drug Administration • National Cancer Institute • National Institute for Occupational Safety and Health
National Institute of Environmental Health Sciences • National Institute of Standards and Technology • National Institutes of Health
National Library of Medicine • Occupational Safety and Health Administration

Interagency Coordinating Committee on the Validation of Alternative Methods

- National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (**NICEATM**), supporting 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.

ICCVAM 2020-2021 Biennial Progress Report

https://ntp.niehs.nih.gov/go/2021iccvamreport

7 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

10 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 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: NCATS, Tox21 Representatives

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

Validation Workgroup Roster

ICCVAM Sponsor Agencies: CPSC, FDA, NIST

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Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies

A Report of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Validation Workgroup

- Underlying principles from OECD 34 are upheld in this new report, similar to the 1997 report.
- Introduce the “context of use” terminology.
- Emphasize that validation process should be flexible and adaptable.
- Emphasize the need for communication because regulatory needs vary across the federal agencies.

"Advances in science and technology have not been effectively leveraged to predict adverse human health effects"

Help end-users guide the development of the new methods

Use efficient and flexible approaches to establish confidence in new methods

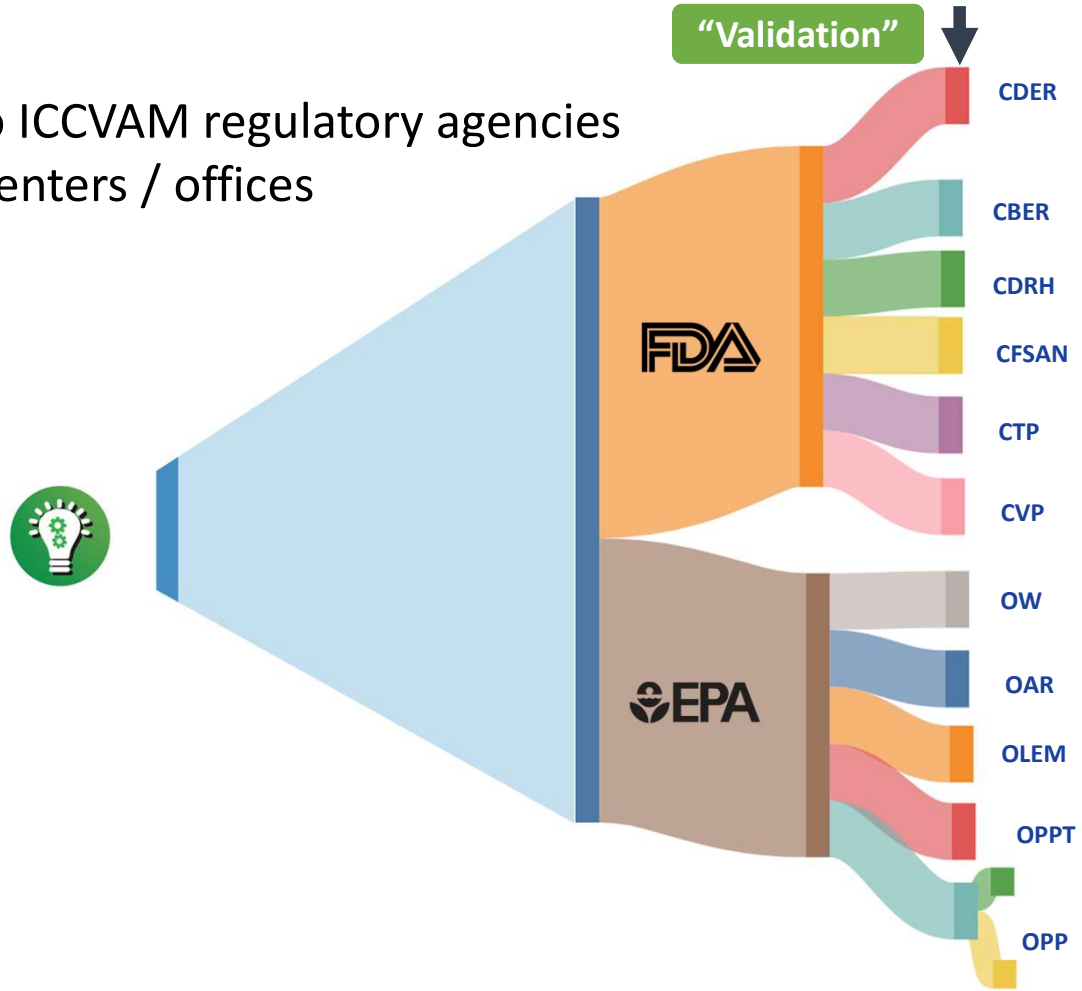
Encourage the adoption of new methods by federal Agencies and regulated industries

https://ntp.niehs.nih.gov/go/natl-strategy

"Advances in science and technology have not been effectively leveraged to predict adverse human health effects"

https://ntp.niehs.nih.gov/go/natl-strategy

Example of two ICCVAM regulatory agencies with multiple centers / offices



Small Molecule Drugs

Biologics

Devices

Food / Cosmetics

Tobacco Products

Veterinary Products

Water Pollutants and Contaminants

Air Pollutants

Hazardous Waste

Industrial Chemicals

Pesticides /Human Health

Pesticides / Eco Tox

From

- Centralized ("VAMs")
- One Size Fits All
- Binary Status (Validated / Not)
- Stand Alone

TRANSITION

Towards

- Decentralized (End Users)
- Fit for Purpose
- Evolving Confidence
- Integrative

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https://doi.org/10.1007/s00204-022-03365-4

REVIEW ARTICLE

A framework for establishing scientific confidence in new approach methodologies

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Unclassified ENV/JM/MONO(2005)14

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

18-Aug-2005

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

OECD SERIES ON TESTING AND ASSESSMENT
Number 34

GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT

ENV/JM/MONO(2005)14
Unclassified

Arch Toxicol (2018) 92:611–617
https://doi.org/10.1007/s00204-017-2097-4

REGULATORY TOXICOLOGY

Standardisation of defined approaches for skin sensitisation testing to support regulatory use and international adoption: position of the International Cooperation on Alternative Test Methods

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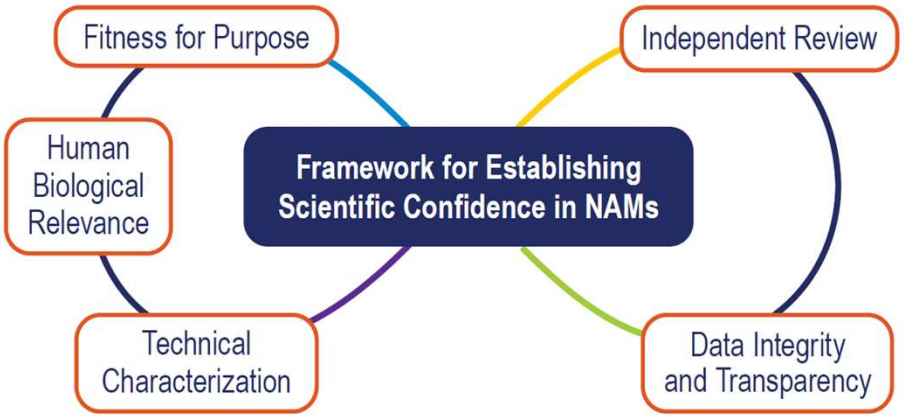
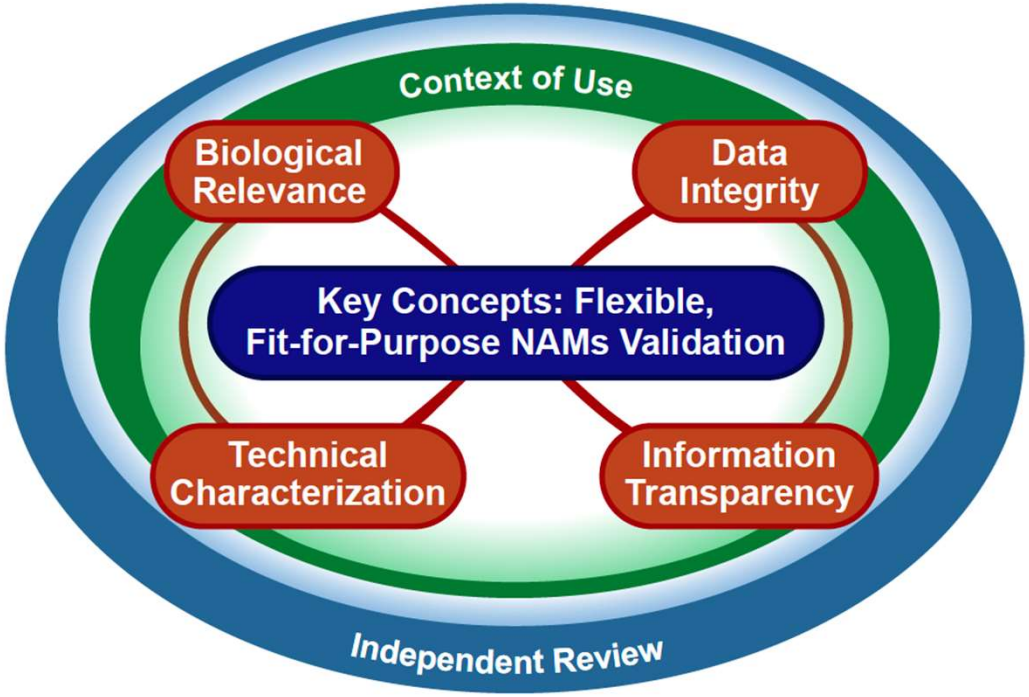


van der Zalm et al. 2022 Arch Tox

A. Harrill, EPA NAMs Conference, Oct 2022

Key Concepts to Consider During Development and Implementation of Flexible, Fit-for-Purpose NAMs Validation Strategies

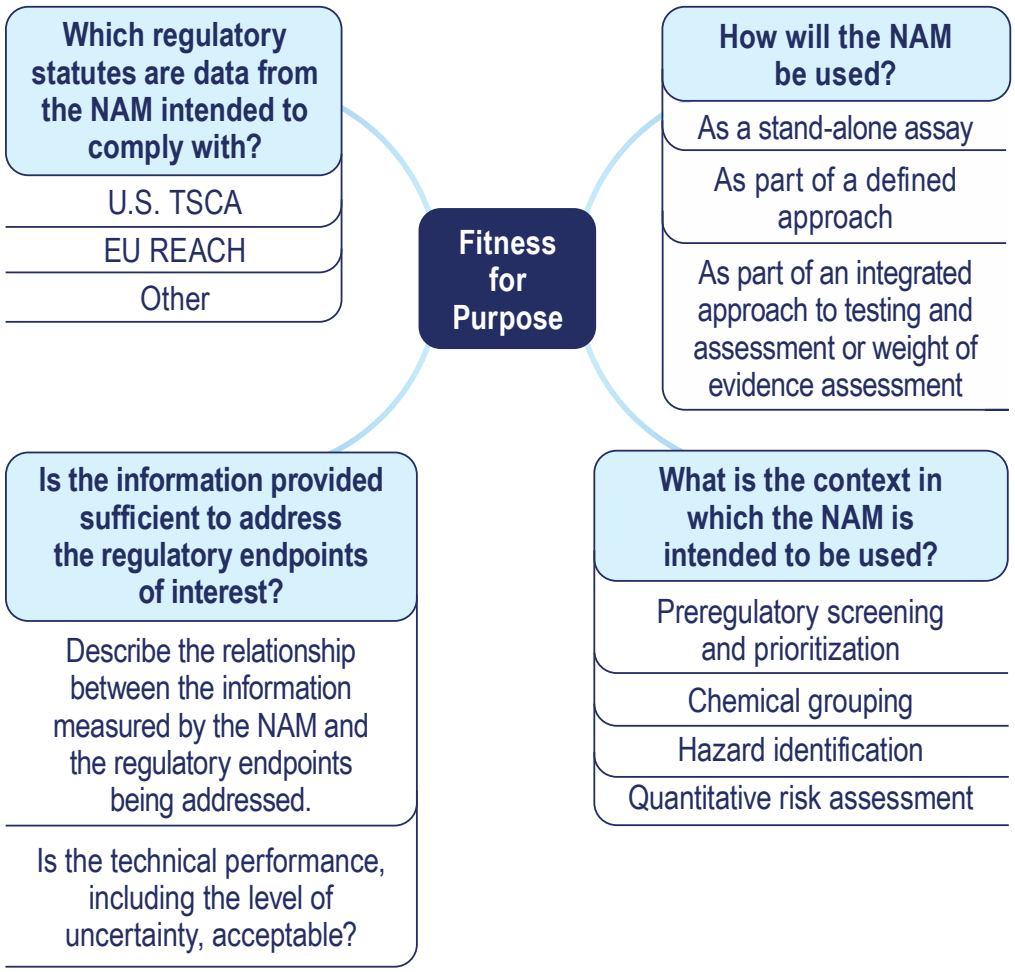


Final Draft ICCVAM Validation Report, Figure 1
(adapted from van der Zalm et al. 2022 Arch Tox)

https://ntp.niehs.nih.gov/go/ICCVAM-submit

Context of Use

Purpose = Context of Use



van der Zalm et al. 2022 Arch Tox

(Human) Biological Relevance

- Similarities between the physiology of, or the biology measured by, the test system, and human biology
  - ✓ Consider human dosimetry modelling, cell types used, or the structure of the target organ/tissue
- Concordance with human responses

- Establishing biological relevance of a method can be used to benchmark its performance

Biological relevance

- Traditional animal test methods should not be assumed to provide data relevant to human biology or mechanisms of toxicity and be the "right" answer to determine if another method is valid.
- When using benchmark animal data:
  - Relevance to predict human effects should also be considered, where possible (in the case of human health endpoints)
  - Variability of animal data should be characterized and considered when evaluating alternative approaches
- Instead, accuracy can be demonstrated by considering:

↳ Consistency across methods/approaches

↳ Ability to identify positive and negative reference chemicals

↳ Greater emphasis on biological relevance and reproducibility

Examples of Endpoints where Biological and Mechanistic Relevance of NAMs has been Demonstrated to Support Regulatory Applications

Endpoint	Summary	Reference
Skin sensitization	The endpoint has a well-developed human relevant AOP to which defined approaches combining several NAMs are mapped and described in OECD Guideline 497.	Kleinstreuer et al., 2018; OECD, 2021a
Endocrine disruption	Established pathway models using complementary NAMs as part of an integrated strategy are available for estrogen and androgen receptor activity. EPA accepts these NAMs for Tier 1 screening in the Endocrine Disruptor Screening Program.	Judson et al., 2015; Kleinstreuer et al., 2017; EPA, 2023
Developmental neurotoxicity	Limited AOPs exist for this complex endpoint. Instead, a battery of NAMs covering critical processes of human neurodevelopment has been developed. An OECD GD on the battery is available that includes integrated approaches to testing and assessment (IATA) case studies.	Crofton and Mundy, 2021; OECD, 2022a; OECD, 2023
Inhalation toxicity	An alternative approach using an in vitro human-cell based assay and computational modeling was used to characterize the hazard of chlorothalonil and derive a point of departure for use in EPA human health risk assessment. This approach was also published as an OECD IATA case study.	Corley et al., 2021; EPA, 2021c; OECD, 2022b

Draft ICCVAM Validation Report, Table 3

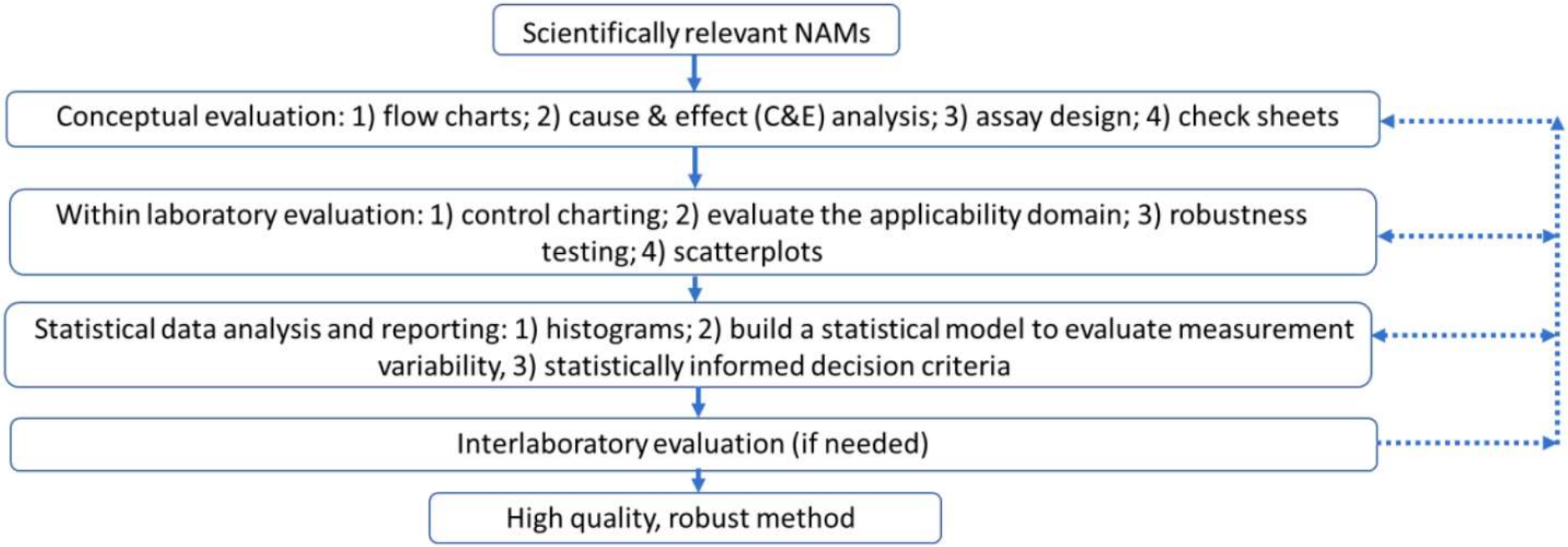
Technical Characterization

- Describe:
  - intra-laboratory reproducibility
  - transferability
  - applicability domain
  - reference chemicals and controls
  - limits of detection and quantification

- Data reporting should allow for evaluation of the method, including:
  - protocol
  - equipment
  - computational models being used

- What is considered acceptable may depend on the method being evaluated and its intended use

Framework for Developing Robust NAMs



Draft ICCVAM Validation Report, Figure 2
(reprinted with permission from Petersen et al. 2022 ALTEX)

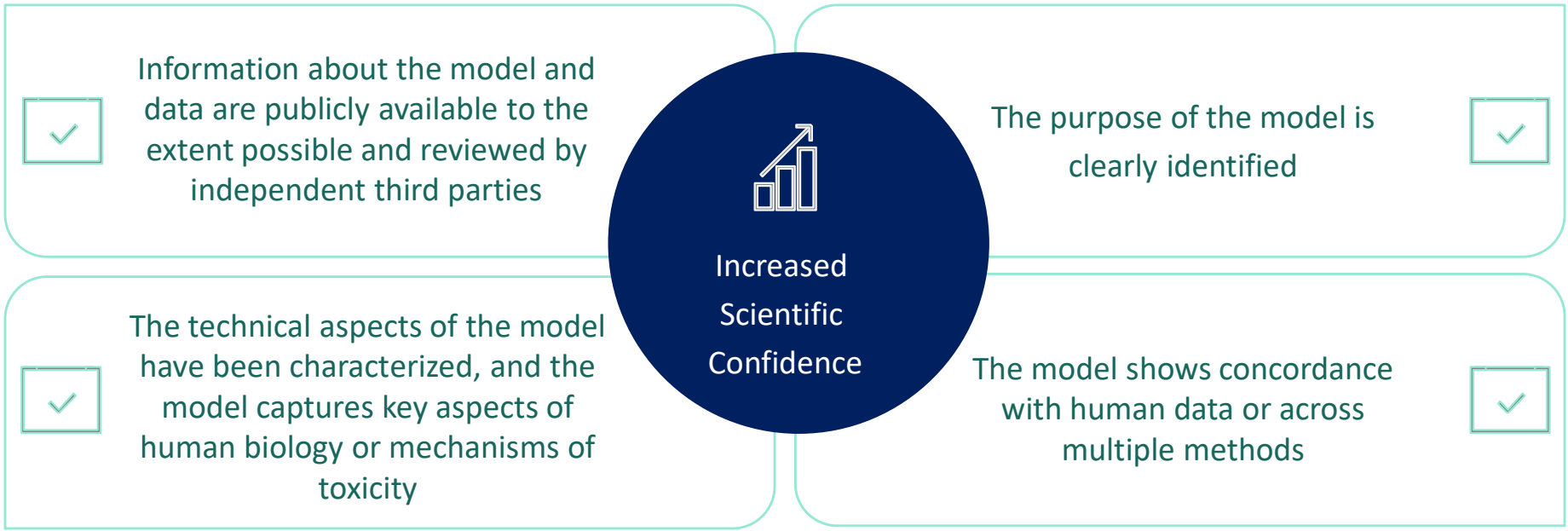
Data Integrity and Information Transparency

- Assess integrity and credibility of the raw data to the final report
- Communicate transparently and publicly
- Assess and describe the uncertainties and limitations
- Independently reproduce data
  - External implementation and training of the models
  - Processing of the raw data
  - Replicate predictions obtained in the validation study

Draft ICCVAM Validation Report Tables

- Existing U.S. and International Documents Related to Validation, Qualification, and Regulatory Use of NAMs
- Manuscripts Produced by ICCVAM Workgroups that Provide Details about Agency Testing Needs for Selected Topics
- Examples of Endpoints where Biological and Mechanistic Relevance of NAMs has been Demonstrated to Support Regulatory Applications

In summary…



Confidence in a method should be determined with the species of interest (humans) in mind

Timeline

- Scope and Charges were developed in March 2021.
- The document was collaboratively developed by all participating federal agencies.
- Completed the draft version of the document in August 2023.
- The Federal Register notice was published on August 10th, 2023.
- The document went out for public comment on August 10th, 2023.
- Public comment period ended September 5th, 2023.
- Input from Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) on September 21st, 2023
- Revised document currently under final review by all participating federal agencies
- Anticipate final report published by ICCVAM in early 2024

Future Activities

- Method Developers Forum
  - Opportunity for discussion between regulators and method developers.
  - Method developers may utilize the report as a template to follow.

Method Developers Forum (MDF)

- A proactive effort to highlight the recommendations detailed within the VWG report (Figure 1) and provide an opportunity for NAMs developers to interact with federal agency (and other) end users.
- Anticipate holding approximately 2-3 MDFs per year.
- Each iteration will focus on a specific endpoint/toxicity.
  - Industry and regulatory stakeholders summarize their information needs and decision frameworks for the specific endpoint/toxicity in pre-recorded webinars.
  - Developers demonstrate how their methods address the topic of interest in an interactive webinar, using the Key Concepts in Fig 1 as a presentation “template”.
  - The first MDF will focus on NAMs for **carcinogenicity** testing.

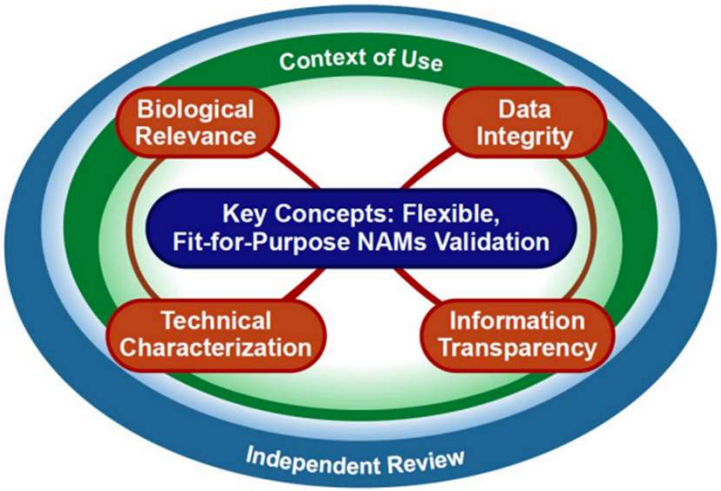


Figure 1. Key concepts to consider during development and implementation of flexible, fit-for-purpose NAMs validation strategies. Adapted from van der Zalm et al. (2022).