A Modern Framework to Establish Scientific Confidence in New Approach Methodologies (NAMs)

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ABSTRACT

Current processes to validate new approach methodologies (NAMs) are costly, time-consuming, and do not necessarily produce methods that are fit for regulatory purposes. This poster builds on previous efforts from the Organisation for Economic Co-operation and Development and the International Cooperation on Alternative Test Methods to propose a modern, flexible framework comprising five essential elements to establish scientific confidence in NAMs for regulatory use: fitness for purpose, human biological relevance, technical characterization, data integrity and transparency, and independent review.

Updates to the current process are based on the recognition that:

(a) the relevance of the NAM results need not be determined through direct alignment with the results of the traditional animal test method, and instead may be determined through alignment with, or fidelity to, human biological understanding

(b) the NAM should not be required to replace the traditional animal test method one to one, nor produce the same information generated by the traditional animal test method

(c) the currently accepted levels of reproducibility in traditional animal test methods can be used to inform performance benchmarks for NAMs

(d) ring trials may not be necessary for the assessment of the reproducibility of a NAM

(e) preferably before a NAM is developed, its purpose should be clearly defined and discussed amongst the method developer, regulators, and the regulated industry to ensure the production of NAMs that are fit for purpose

FRAMEWORK COMPRISING FIVE ESSENTIAL ELEMENTS

Fitness for purpose

- Define which regulatory statute the data from the NAM are intended to comply with.
- Ensure the NAM provides the information that is needed by end-users to come to a conclusion for the chemical under consideration:
  - Define how the information measured by the NAM relates to the regulatory endpoint of interest
  - Define the acceptable level of uncertainty for the specified purpose.
- Define the manner in which the NAM will be incorporated into the assessment.
- Define the context(s) in which the NAM is intended to be used.
- Provide information about the various adverse human health endpoint(s), exposure pathway(s), life stage(s) and population(s) that will be addressed by the NAM.

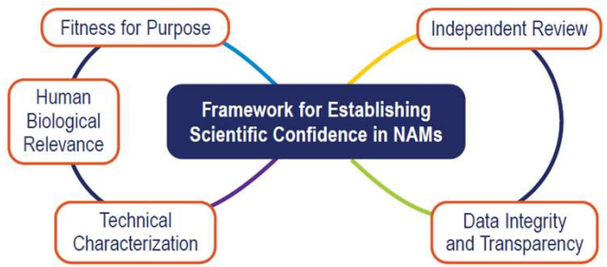

Figure from van der Zalm et al. 2022

Human biological relevance

- Demonstrate the similarities between the physiology of the test system or the biology measured by the test system, and human biology. Confidence in a NAM is bolstered when it adequately reflects human biological understanding.
- For endpoints where human data or reference chemicals are available, demonstrate concordance of the NAM with human responses to build confidence in its human biological relevance.
- When applicable, evaluate the traditional animal test method(s) taking into account the human biological relevance. When comparisons are appropriate, demonstrate that the NAM reflects human biological understanding as well as or better than the traditional animal test method.

Technical characterization

- Evaluate the protocol, the equipment used, and any computational models being used for endpoint prediction and/or in vitro to in vivo extrapolation.
- Assess and describe the intra-laboratory reproducibility, transferability (where applicable), applicability domain, associated reference chemicals and controls, and limits of detection and quantification.
- Where relevant, assess and describe the accuracy of the NAM.

Independent review

- Determine the appropriate level of external review necessary for a NAM. Peer review and publication of a NAM's human biological relevance, fitness for purpose, and technical characterization is encouraged. In certain cases, NAMs may be reviewed by independent third parties.

Data integrity and transparency

- Demonstrate the integrity and credibility of the data submitted for assessment and peer review.
- Communicate transparently and, as far as possible, make publicly available information about a NAM's relevance to human biology, fitness for purpose, and technical characterization, as well as the principles of the NAM, the protocol, and reporting standards.
- Assess and describe the uncertainties and limitations associated with the NAM.

HUMAN BIOLOGICAL RELEVANCE ASSESSMENT CASE STUDY: EYE IRRITATION

Depth of Injury Model

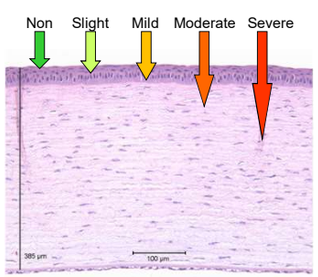

Image modified from Scott, et al., 2010

The scientific validity of available *in vitro/ex vivo* methods and the *in vivo* method were assessed by comparing their reproducibility, and investigating relevance to human biology and mechanisms of eye irritation (Clippinger et al. 2021).

Authors concluded that many available *in vitro* and *ex vivo* models are more human relevant and robust than the rabbit test because they include one or more of the following properties:

a) more closely model potential exposures in humans and allow for precise dosing
b) model (human) corneal tissue barrier functions and penetration kinetics
c) include relevant cell types within each of the tissue layers
d) provide quantitative results
e) are reproducible
f) discriminate a range of cytotoxic responses within each layer

Considering the variability of the currently used rabbit test (Luechtefeld et al. 2016) and an understanding of human biology and mechanisms of eye irritation, to best protect human health, the authors concluded that data from the *in vitro/ex vivo* methods should be considered applicable for use at this time.

Schematic depiction of the human eye

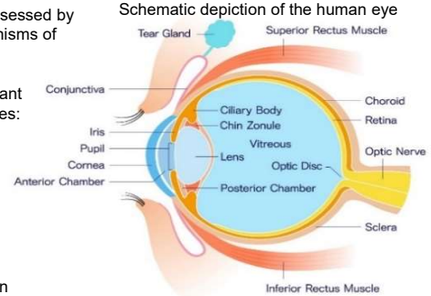

Image purchased from iStock

CONCLUSIONS

Use of the framework will enable a streamlined confidence building process that allows for the timely uptake of fit for purpose and biologically relevant NAMs that can be used in the regulatory decision making process as appropriate within each agency's regulatory framework.

Instead of relying on a direct comparison to the currently used animal test method, the framework encourages a holistic assessment of a chemical's ability to cause toxicity in humans by relying on NAMs that reflect human biological understanding. Case studies demonstrate how to implement this aspect of the framework (eye irritation [left], inhalation [case study in progress]).

Use of the framework should provide better coverage of human biology and mechanisms of toxicity, increase confidence in the appropriate use of NAMs, and accelerate industry uptake and regulatory acceptance of relevant and reliable NAMs, thereby providing better protection of human health.

Disclaimer: The views expressed in this poster are those of the authors and do not necessarily represent the views or policies of their respective employers or their stakeholders.

References: Luechtefeld T, Maertens A, Russo DP, Rovida C, Zhu H, Hartung T. Analysis of Draize eye irritation testing and its prediction by mining publicly available 2008-2014 REACH data. ALTEX. 2016;33(2):123-134; Clippinger AJ, Raabe HA, Allen DG, et al. Human-relevant approaches to assess eye corrosion/irritation potential of agrochemical formulations. Cutan Ocul Toxicol. 2021;40(2):145-167; van der Zalm AJ, Barroso J, Browne P, et al. A framework for establishing scientific confidence in new approach methodologies. Arch Toxicol. 2022;10.1007/s00204-022-03365-4.

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