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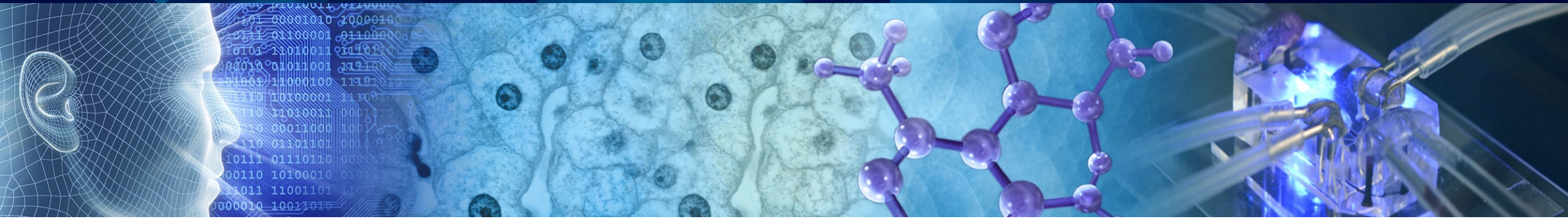


Building models for regulatory application: understanding challenges and increasing trust

Nicole C. Kleinstreuer, PhD

National Interagency Center for the Evaluation of Alternative Toxicological Methods

NICEATM and ICCVAM

- 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.

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

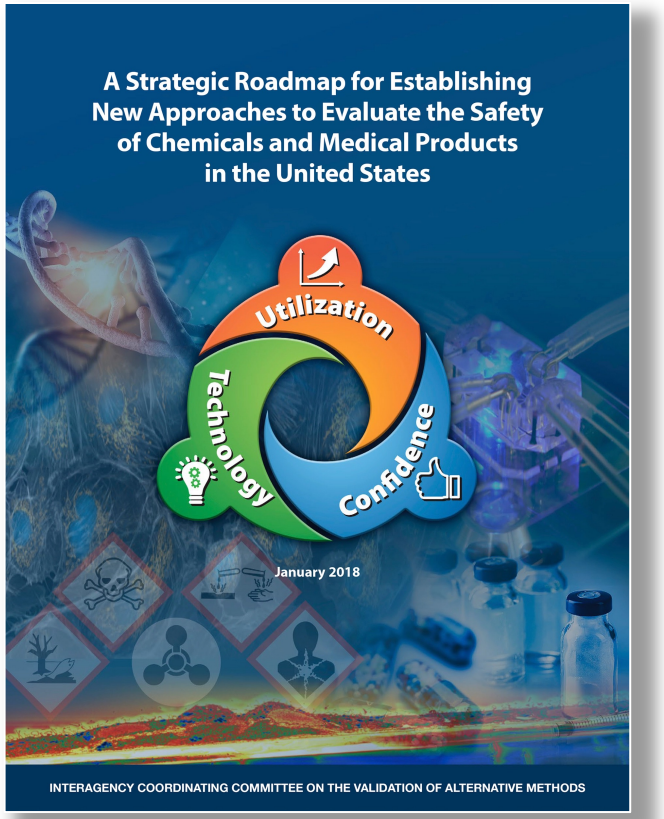
"Advances in science and technology have not been effectively leveraged to predict adverse human health effects"

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

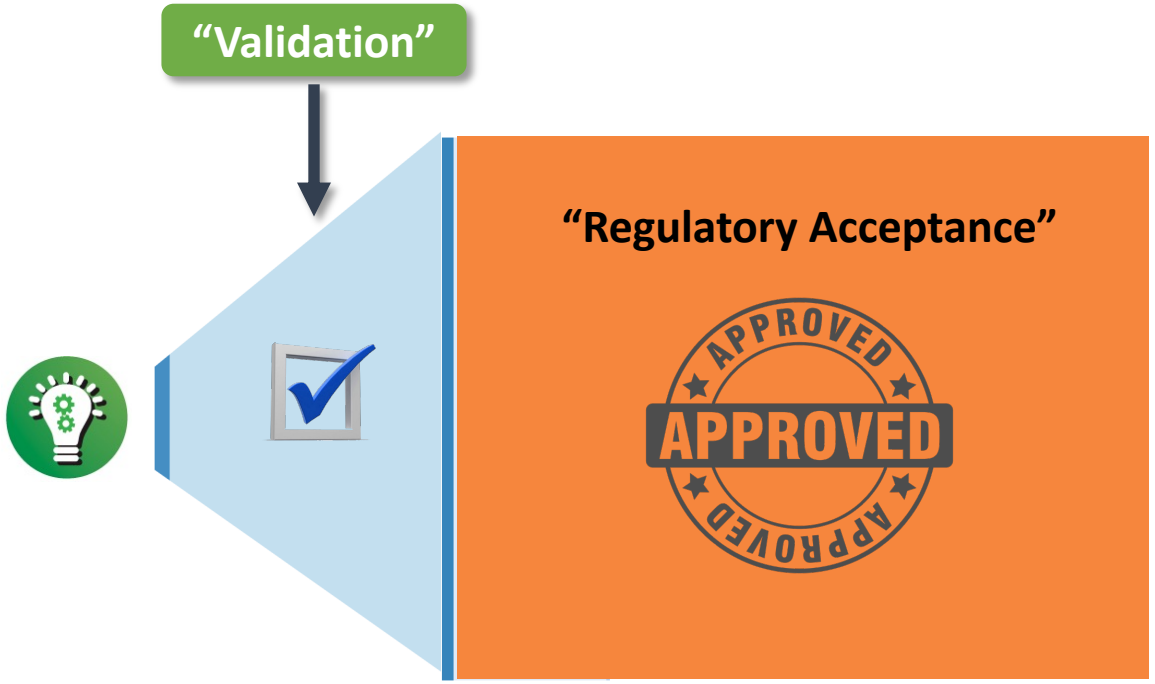
"Advances in science and technology have not been effectively leveraged to predict adverse human health effects"



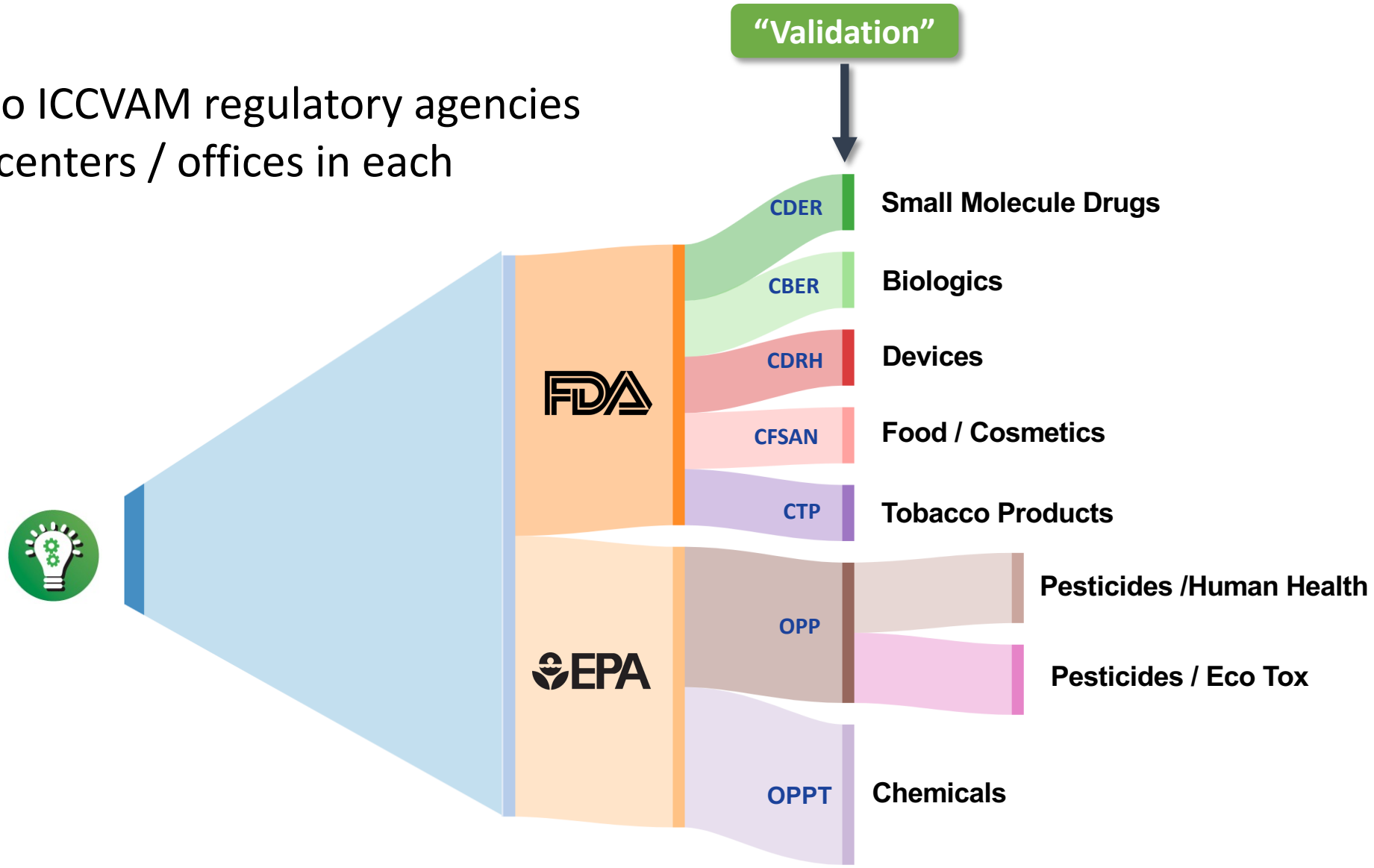
Help end-users [illegible] development of the new m[illegible]

Use eff[illegible]nt an[illegible]e ap[illegible]aches to establis[illegible]nce [illegible]new [illegible]thods

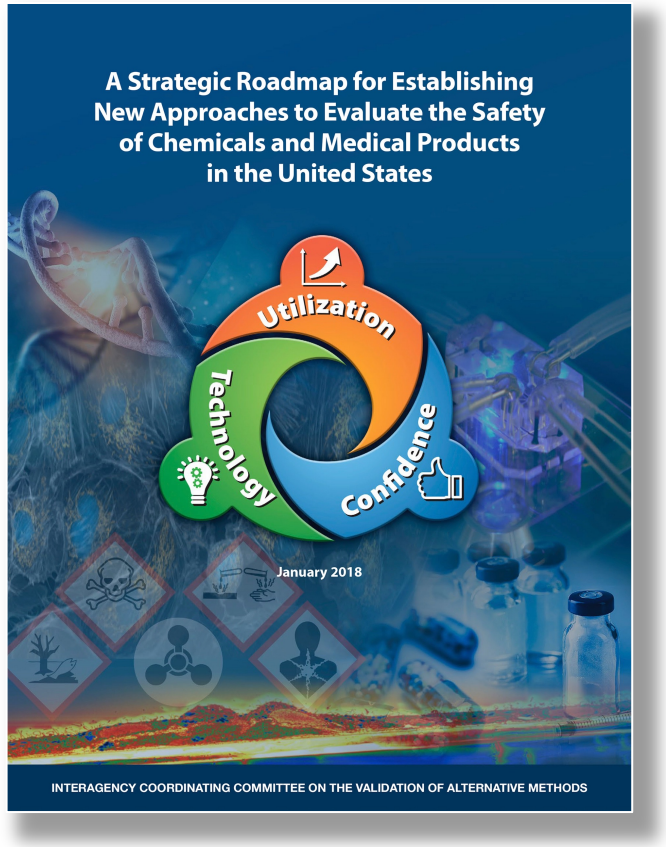
Encourage t[illegible] new methods by federal Agencies and regulated industries


"Validation"
"Regulatory Acceptance"
APPROVED
APPROVED
APPROVED

Example of two ICCVAM regulatory agencies with multiple centers / offices in each



The "3Cs"



Communication

Collaboration

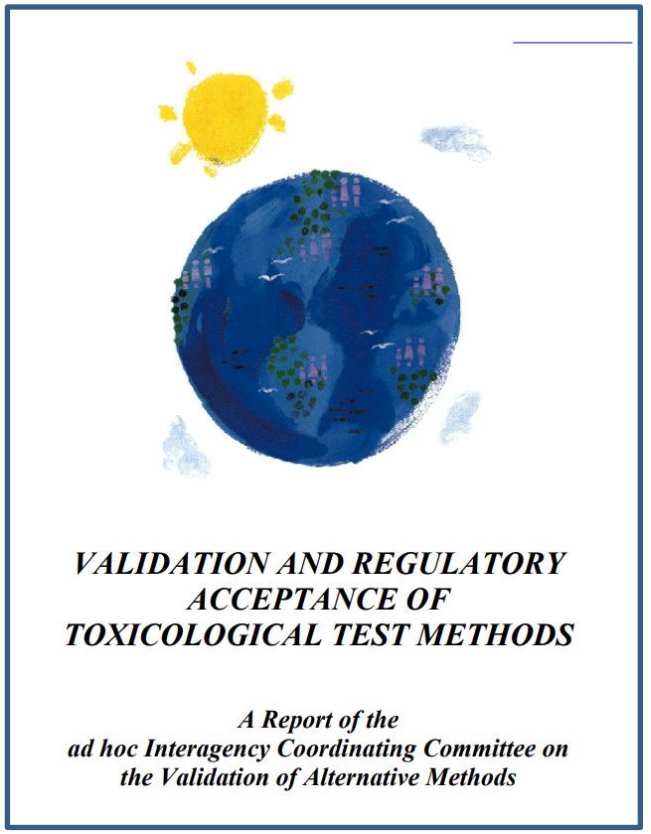
Commitment

ICCVAM: Validation Workgroup

Updating ICCVAM Guidance on Validation

ICCVAM Sponsor Agencies:
CPSC, FDA/CFSAN

Participating Agencies:
EPA/OPP, EPA/ORD, ATSDR, VA ORD, DOD, NIST, OSHA, NIEHS, NIH, FDA/CDER,/CTP,/OCS,/CDRH



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National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina 27709

National Institutes of Health
U.S. Public Health Service
Department of Health and Human Services

March 1997

TRANSITION

From

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

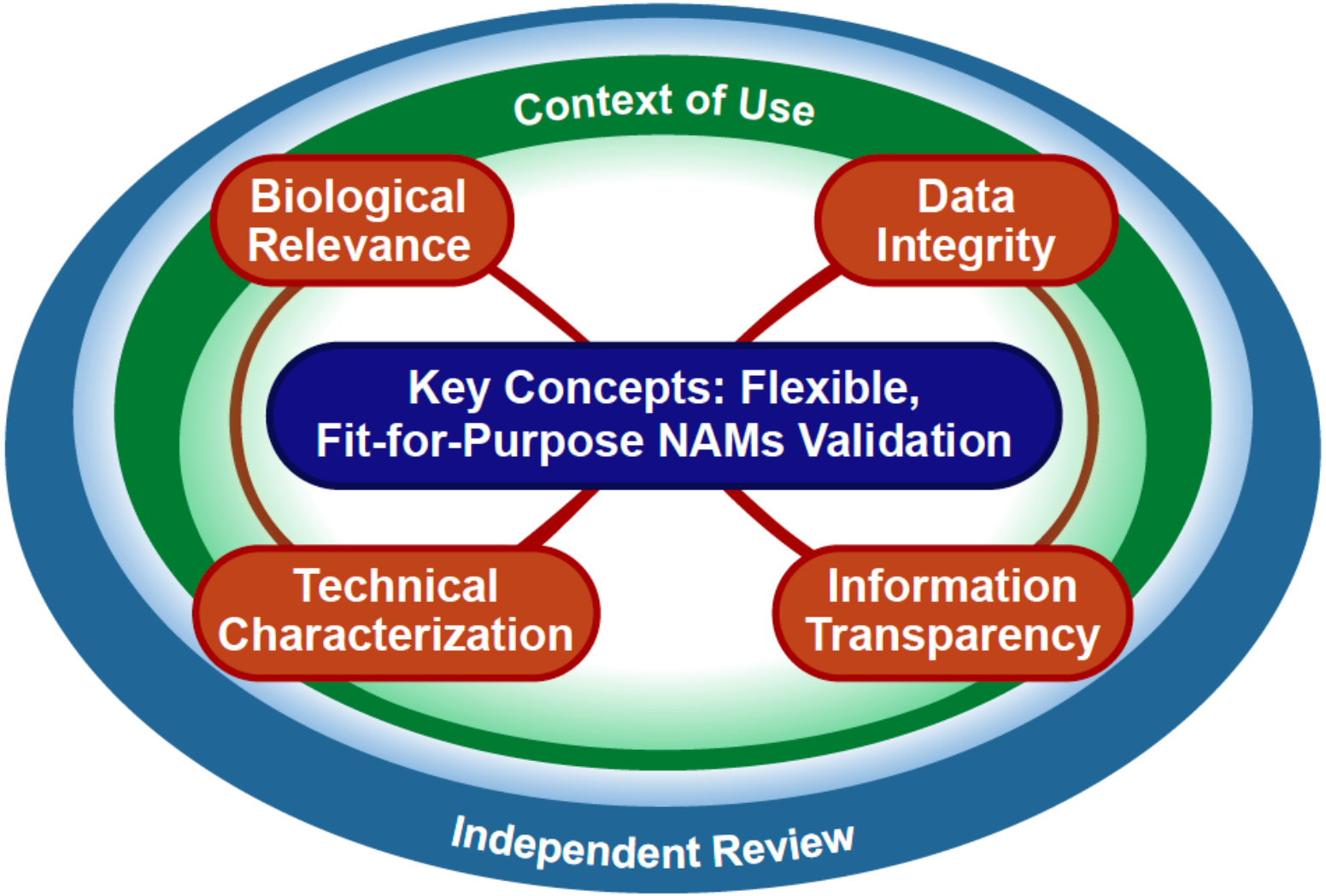
Towards

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

New Guidance from ICCVAM

- Underlying principles from OECD 34 remain the same in this new Guidance.
- Introduce the “context of use” terminology
- New guidance will emphasize that processes used to establish confidence should be flexible and adaptable.
- Emphasize the need for communication because regulatory needs may vary across the federal agencies

Updated ICCVAM Validation Guidance: Coming Soon!



Topics Covered in the New Guidance

Foster the use of efficient, flexible, and robust practices to establish confidence in new methods

- Clearly delineate testing requirements and context of use
- Promote the use of new approaches for establishing confidence
- Utilize public workshops and/or public-private partnerships to promote cross-sector communication and cooperation
- How new principles for establishing confidence can fit into a globally harmonized approach to allow for continued mutual acceptance of data
- Reference to existing and well-vetted documents (e.g., GIVIMP, OECD GD34, GD69 on QSAR Validation, FDA Guidance for Industry, etc.)

Topics Covered in the New Guidance

- Relevance of New Approach Methods (e.g. biological plausibility, mechanistic relevance)
- Importance of Quality Reference Data and Role of Legacy Animal Data
- Discussion of "Good or Better Standard" for qualification/validation.
- Technical Considerations
  - Examination of best practices for quality and quality systems development
  - Assessment of key sources of variability in the NAM
- Incorporation of selected data quality tools such as:
  - Building a statistical model
  - Setting specifications

van der Zalm et al. 2022; Petersen et al. 2022

Role of ICCVAM

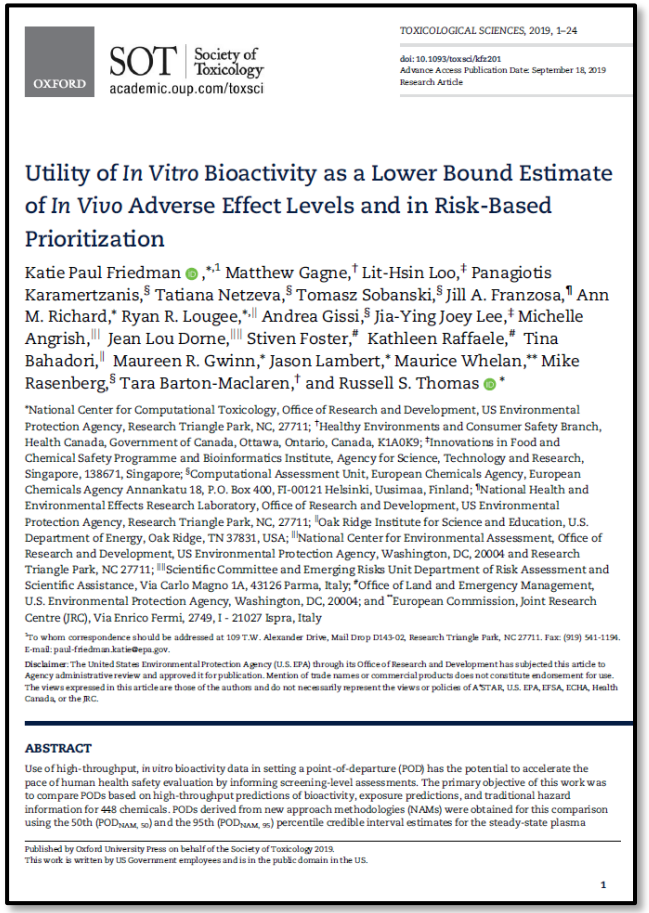
- Assure an independent process for establishing confidence
- Advise federal agencies on different strategies for establishing confidence
- Facilitate cross-agency collaborations through work group/conferences
- Encourage global communication/harmonization on criteria used to establish confidence through conferences, seminars and meetings

Next Steps Prior to Finalization

- Format and organization of the document still under consideration.
- Input from the ICCVAM Federal Agencies still being incorporated through the VWG
- Draft document will be sent to ICCVAM agencies for review and sign off.
- Stakeholders will have opportunity to comment on the document.

Regulatory Focused Case Study on Bioactivity as a Point-of-Departure

APCRA
ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT



OXFORD | SOT Society of Toxicology
academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 2019, 1–24
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

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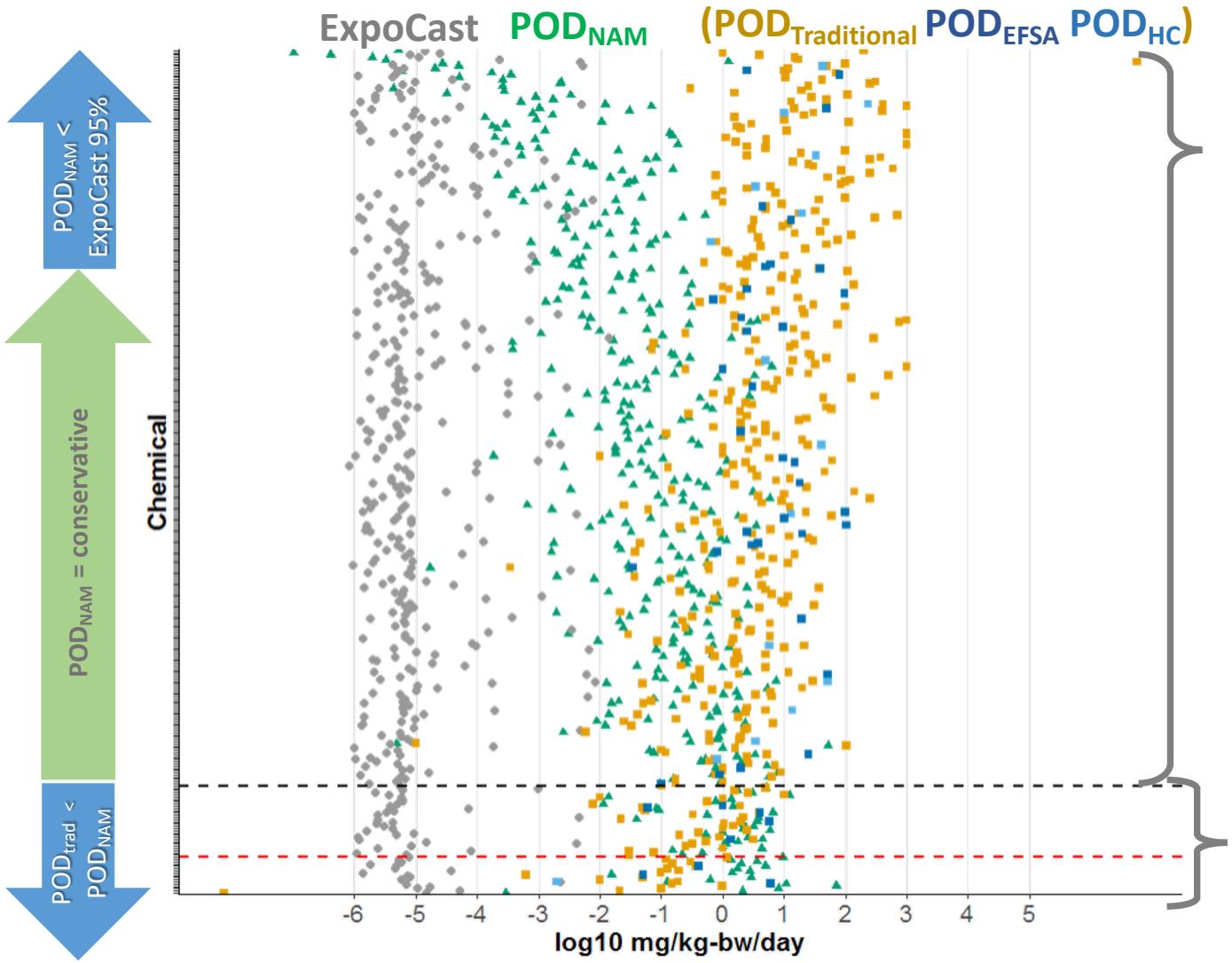
ABSTRACT

Use of high-throughput, *in vitro* bioactivity data in setting a point-of-departure (POD) has the potential to accelerate the pace of human health safety evaluation by informing screening-level assessments. The primary objective of this work was to compare PODs based on high-throughput predictions of bioactivity, exposure predictions, and traditional hazard information for 448 chemicals. PODs derived from new approach methodologies (NAMs) were obtained for this comparison using the 50th ($POD_{NAM,50}$) and the 95th ($POD_{NAM,95}$) percentile credible interval estimates for the steady-state plasma

Published by Oxford University Press on behalf of the Society of Toxicology 2019.



For ~89% of the chemicals, POD_{NAM} was conservative.

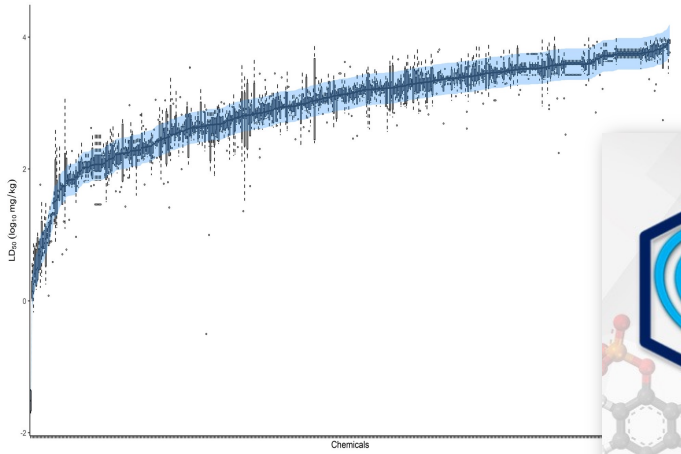
(~100-fold on average), but less conservative than a TTC

Chemicals where POD_{NAM} was not conservative enriched in OPs/carbamates

Courtesy of Rusty Thomas

Reference Data Variability

Data-driven Confidence Intervals for Model Evaluation/Predictions



OPERA
OPEn (q)saR App

Analyzing sources of variability in acute oral toxicity data & applying 95% confidence interval to predictions

	0	5	50	300	500	2000	5000 mg/kg
VT	0	0	1	1	1	1	1
NT	1	1	1	1	1	0	0
EPA	0	0	1	1	0	0	0
GHS	0	0	1	0	0	0	0
LD50	0	0	1 (160 (-0.3))	1 (316 (+0.3))	1 (613)	0	0
WoE	**1**	**1**	**5**	**4**	**3**	**1**	**1**

	Very Toxic		Non-Toxic		EPA		GHS	
	Train	Eval	Train	Eval	Train	Eval	Train	Eval
Sensitivity	0.87	0.70	0.88	0.67	0.81	0.62	0.80	0.58
Specificity	0.99	0.97	0.97	0.90	0.92	0.86	0.95	0.90
Balanced Accuracy	0.93	0.84	0.92	0.78	0.87	0.74	0.88	0.74
***In vivo* Balanced Accuracy**	0.81		0.89		0.82		0.79	

	LD50 values		LD50 values
	Train	Eval	***In Vivo***
R2	0.85	0.65	0.80
RMSE	0.30	0.49	0.42

CATMoS QSAR predictions perform just as well as replicate *in vivo* data at predicting oral acute toxicity outcome

Karmaus et al. Toxicol Sci. 2022; Mansouri et al. EHP 2021

Human Relevance

Prior GHS category	1	2A	2B	NC
1 (serious eye damage)	73%	16%	0%	10%
2A (irritant)	4%	33%	4%	59%
2B (mild irritant)	0%	4%	16%	80%
NC (non-irritant)	1%	4%	2%	94%

Adapted from Luechtefeld et al., ALTEX 33(2), 2016.

Consider strengths and limitations of all available methods with respect to:

- their relevance to human ocular anatomy
- the mechanisms of eye irritation/corrosion in humans

Clippinger et al. 2021 Cut Ocu Tox

Assessing approaches for eye corrosion/irritation potential

- The rabbit test should not be used as a reference method to demonstrate the validity of *in vitro/ex vivo* assays
- *In vitro/ex vivo* methods are as or more reliable and relevant than the rabbit test

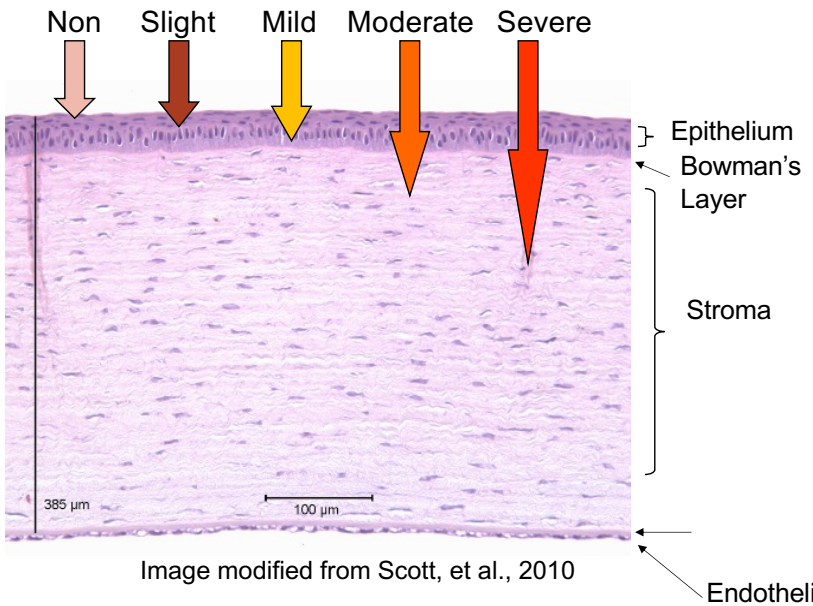


Image modified from Scott, et al., 2010

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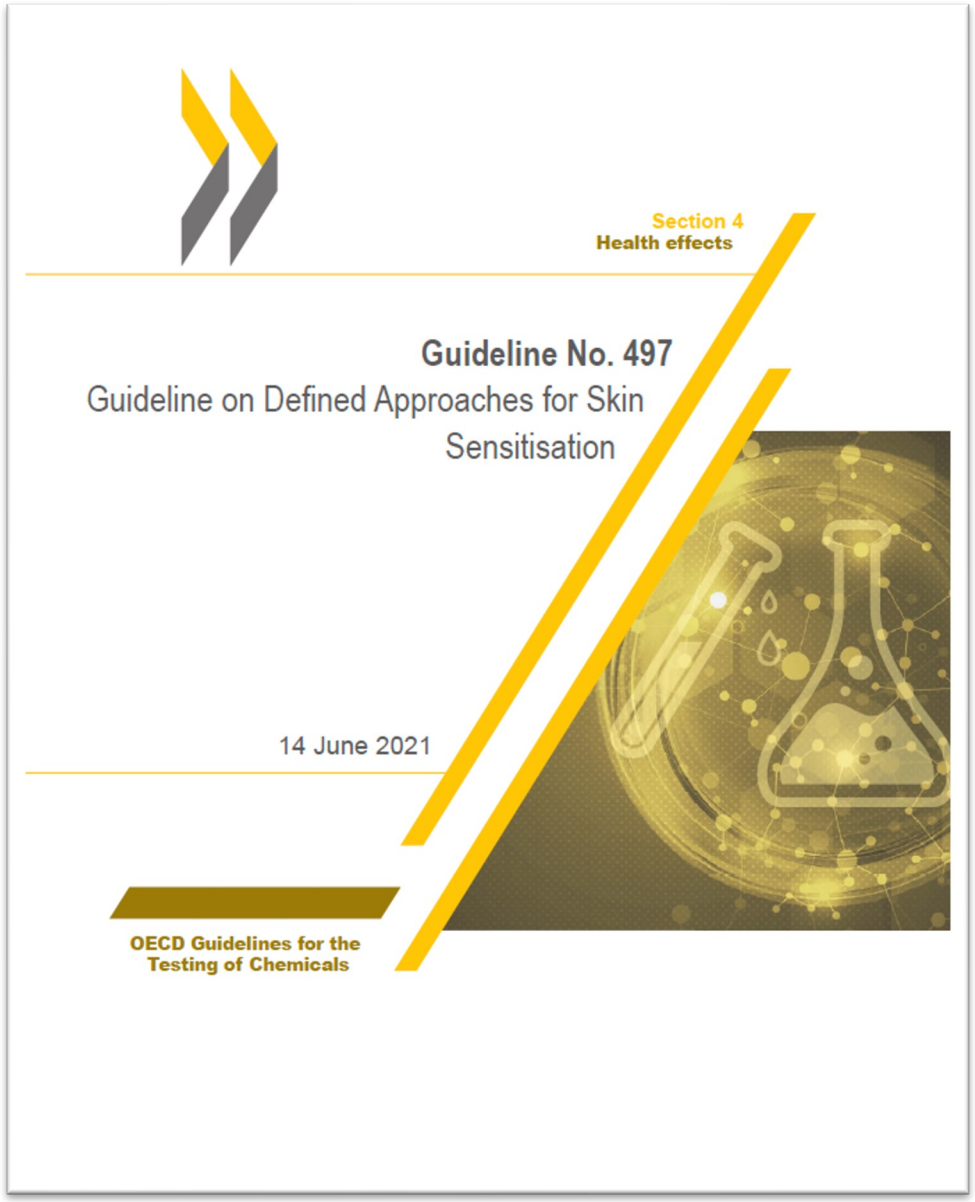
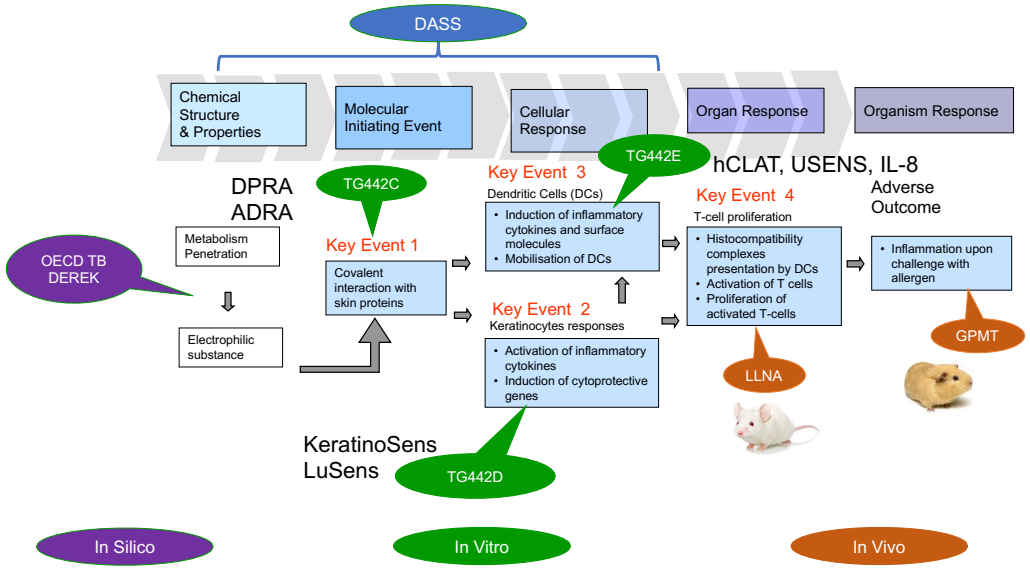
AOP-Anchoring

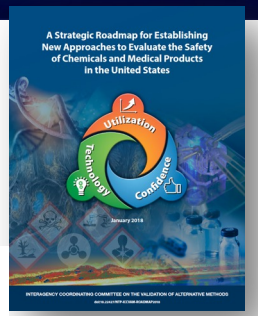




DA/Method	Information Sources	Capability (Hazard and/or Potency)	Hazard Performance vs. LLNA N~168	Hazard Performance vs. Human N~63	GHS Potency Performance vs. LLNA (Accuracy)	GHS Potency Performance vs. Human (Accuracy)
2o3 DA	DPRA, KeratinoSens™, h-CLAT	Hazard	84% BA, 82% Sens, 85% Spec	88% BA, 89% Sens, 88% Spec	-	-
ITSv1 DA	DPRA, h-CLAT, DEREK Nexus v6.1.0	Hazard, Potency (GHS)	81% BA, 92% Sens, 70% Spec	69% BA, 93% Sens, 44% Spec	70% NC, 71% 1B, 74% 1A	44% NC, 77% 1B, 65% 1A
ITSv2 DA	DPRA, h-CLAT, OECD QSAR Toolbox v4.5	Hazard, Potency (GHS)	80% BA, 93% Sens, 67% Spec	69% BA, 94% Sens, 44% Spec	67% NC, 72% 1B, 72% 1A	44% NC, 80% 1B, 67% 1A
LLNA (provided for comparison)	*in vivo*	Hazard, Potency	-	58% BA, 94% Sens, 22% Spec	-	25% NC, 74% 1B, 56% 1A

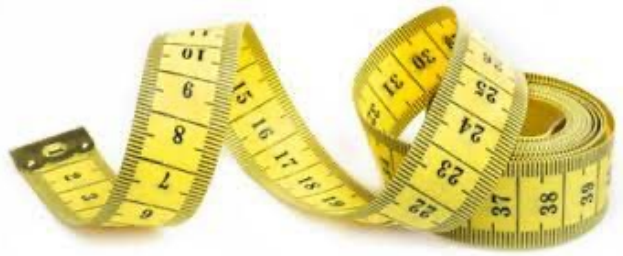
Lessons (Continuously) Learned & Being Applied

- Roadmap 101: Engagement with regulatory stakeholders



- Fit for purpose, performance-based evaluations

- Opportunity for tailored assessments, where data requirements are driven by use cases



- Communication is key

- There are multiple NAMs that are ready for use now!

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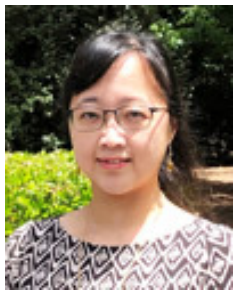
The NICEATM Group



- ICCVAM Agencies
- ICATM Partners
- OECD Secretariat/WGs
- NGO Collaborators

Integrated Chemical Environment

Report for 2020-2021 is out now!

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

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