



**Interagency Coordinating Committee on
the Validation of Alternative Methods**

Encouraging the Use and Adoption of New Methods and Approaches by Federal Agencies and Regulated Industry

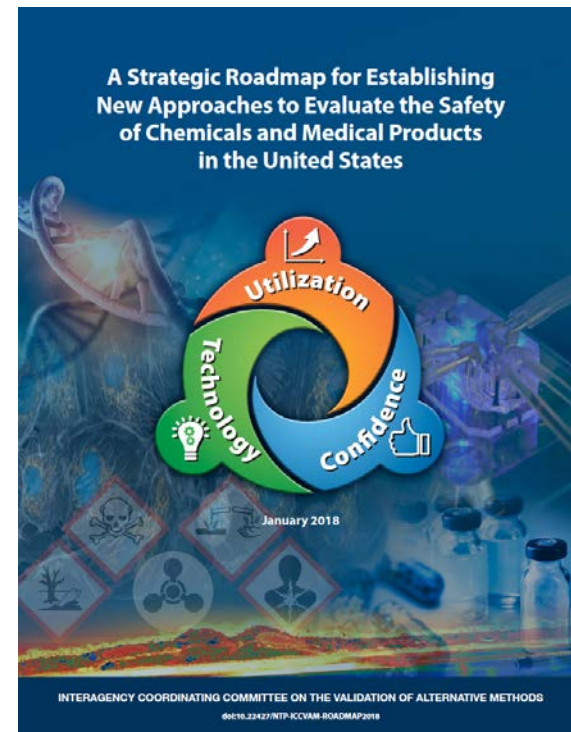
Anna Lowit, PhD
EPA Office of Pesticides Programs

SACATM Meeting
September 6, 2018

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
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences Institute • National
Institute of Standards and Technology • Occupational Safety and Health Administration

Keys to Implementation

- Provide clear language regarding the acceptance of NAMs



EPA Interim Science Policy: Skin Sensitization

- **EPA/OPP and OPPT now accept two non-animal defined approaches as alternatives to the LLNA**
- Covers pesticide actives ingredients, inerts, and mono-constituent industrial chemicals regulated under TSCA

Interim Science Policy: Use of Alternative Approaches
for Skin Sensitization as a Replacement for Laboratory
Animal Testing

DRAFT FOR PUBLIC COMMENT
April 4, 2018

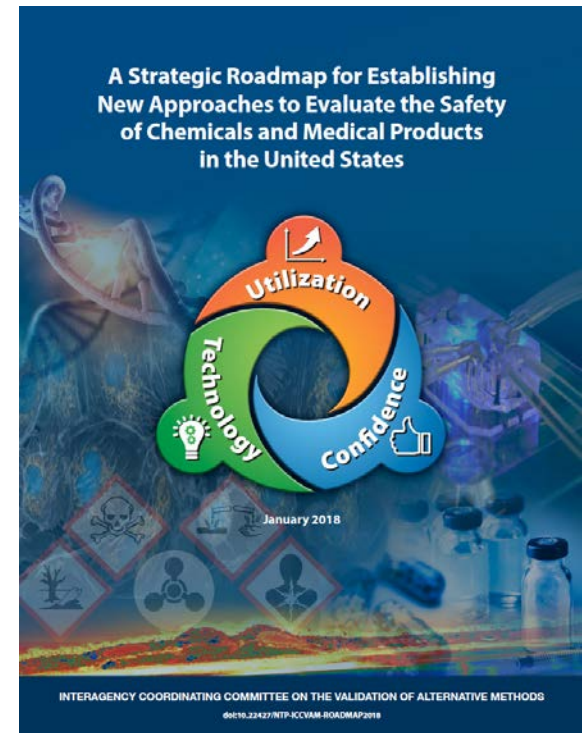
EPA's Office of Chemical Safety and Pollution
Prevention:

Office of Pesticide Programs
Office of Pollution Prevention and Toxics



Keys to Implementation

- Provide clear language regarding the acceptance of NAMs
- Collaborate with international partners to facilitate global harmonization and regulatory acceptance



The International Cooperation on Alternative Test Methods (ICATM)



- Promote international cooperation in the areas of validation studies, independent peer review, and development of harmonized test methods.
- Participation in Validation Management Teams
- October 2018: Workshop on Validation and Establishing Scientific Confidence

Workshop on Acute Toxicity Testing (2017)



~50 international participants

ICATM Regional Updates:

- US, Europe, Japan, Korea, Brazil

Industry Perspectives:

- Current regulatory climate
- GHS additivity calculations

International Harmonization:

- OECD coordination
- ECVAM perspectives on confidence and validation
- Cosmetics Europe skin sensitization collaboration

ICCVAM Participation in OECD TG Program

- An ICCVAM representative will be attending OECD WNT meetings as an official US participant, in support of the national coordinator.
 - Began in April, 2018

International Harmonization

- Standardization of Defined Approaches for Skin Sensitization
- OECD proposal co-led by US, EU, and Canada
- Special OECD-ICATM joint meeting in December, 2017, hosted by EURL-ECVAM.



Arch Toxicol
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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

S. Casati¹ · K. Aschberger¹ · J. Barros¹ · W. Casey² · I. Delgado³ · T. S. Kim⁴ · N. Kleinstreiner² · H. Kojima⁵ · J. K. Lee⁴ · A. Lovit⁶ · H. K. Park⁴ · M. J. Régnibald-Krnel⁷ · J. Strickland⁸ · M. Whelan¹ · Y. Yang⁹ · Valérie Zuang¹

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Abstract Skin sensitisation is the regulatory endpoint that has been at the centre of concerted efforts to replace animal testing in recent years, as demonstrated by the Organisation for Economic Co-operation and Development (OECD) adoption of five non-animal methods addressing mechanisms under the first three key events of the skin sensitisation adverse outcome pathway. Nevertheless, the currently adopted methods, when used in isolation, are not sufficient to fulfil regulatory requirements on the skin sensitisation potential and potency of chemicals comparable to that provided by the regulatory animal tests. For this reason, a number of defined approaches integrating data from these methods with other relevant information have been proposed and documented by the OECD. With the aim to further enhance regulatory consideration and adoption of defined approaches, the European Union Reference Laboratory for Alternatives to Animal testing in collaboration with the International Cooperation on Alternative Test Methods hosted, on 4–5 October 2016, a workshop on the international regulatory applicability and acceptance of alternative non-animal approaches, i.e., defined approaches, to skin sensitisation assessment of chemicals used in a variety of sectors. The workshop convened representatives from more than 20 regulatory authorities from the European Union, United States, Canada, Japan, South Korea, Brazil and China. There was a general consensus among the workshop participants that to maximise global regulatory acceptance of data generated with defined approaches, international harmonisation and standardisation are needed. Potential assessment criteria were defined for a systematic evaluation of existing defined approaches that would facilitate their translation into international standards, e.g., into a performance-based Test Guideline. Informed by the discussions at the workshop, the ICATM members propose practical ways to further promote the regulatory use and facilitate adoption of defined approaches for skin sensitisation assessments.

Keywords Skin sensitisation · Defined approaches · Alternative methods · International standards · Adverse outcome pathway

✉ Valérie Zuang
valerie.zuang@ec.europa.eu

¹ European Commission, Joint Research Centre (JRC), 21027 Ispra, Italy

² National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, National Institute of Environmental Health Sciences, Research Triangle Park, Morrisville, NC 27709, USA

³ BraCVAM, National Institute of Quality Control in Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

⁴ Korean Center for the Validation of Alternative Methods, National Institute of Food and Drug Safety Evaluation, Cheongju, Chungcheongbuk-do, Republic of Korea

⁵ Japanese Center for the Validation of Alternative Methods, National Institute of Health Sciences, Tokyo 158-8501, Japan

⁶ Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington DC 20460, USA

⁷ Environmental Health Science and Research Bureau, Health Environments and Consumer Safety Branch, Health Canada, Ottawa, ON K1A 0K9, Canada

⁸ Integrated Laboratory Systems inc., Research Triangle Park, Morrisville, NC 27709, USA

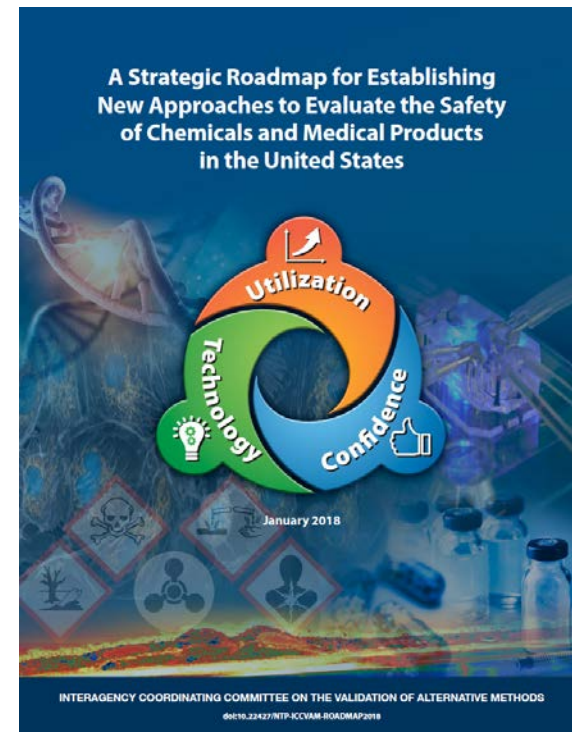
⁹ Institute of Toxicology, Guangdong Provincial Center for Disease Control and Prevention, Guangzhou 510300, China

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- Explore processes to incentivize and promote the use of NAMs



ICCVAM Communities of Practice Webinars

- Opportunity to provide guidance to test method developers and facilitate collaborations that promote the development of new test methods
- Convened annually in January
 - 2018: Machine Learning in Toxicology: Fundamentals of Application and Interpretation
 - 2017: Incorporating Chemical Information: Resources, Limitations, and Characterizing the Domain of Applicability for 21st Century Toxicity Testing
 - 2016: Fundamentals of Using Quantitative Structure–Activity Relationship Models and Read-across Techniques in Predictive Toxicology

Training and Education



The image shows a promotional poster for a training event on the left and a photograph of three scientists in a laboratory on the right. The poster has a red background and features the NURA logo (a white circle with a red starburst pattern) and the text: "NURA", "New Approach Methodology Use for Regulatory Application (NURA):", "Integrating new approaches into your TSCA testing", "October 1-2, 2018", and "Research Triangle Park, NC". A white banner with the word "FREE" in red is positioned in the top right corner of the poster. The photograph shows three people in white lab coats looking at a computer monitor in a laboratory setting with various glassware and equipment.

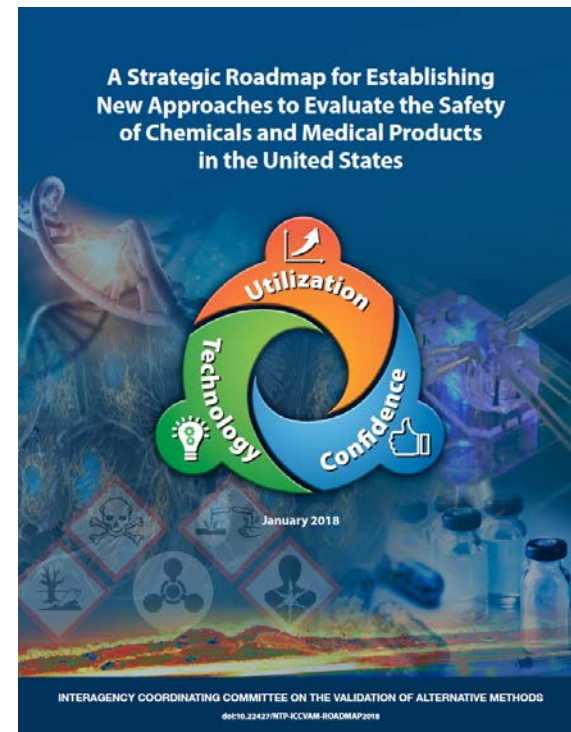
- ICCVAM and NICEATM representatives on the draft program
 - Bert Hakkinen (NLM)
 - Gino Scarano (EPA-OPPT)
 - Nicole Kleinstreuer (NIEHS-NICEATM)
 - Kamel Mansouri (NICEATM Contractor)
- Regulated industry
 - Angus, P&G, Dow

Ongoing Stakeholder Webinar Series

- PETA International Science Consortium series of pre-recorded webinars (n=17) focused on alternative approaches for testing the toxicity of inhaled substances
- International experts from industry, government, and non-profit organizations
- In silico models, in vitro test systems, and integrated approaches to testing and assessment
- This series leverages the collective expertise of many of the participants at the PISC and NICEATM co-organized workshop on alternatives for acute inhalation toxicity testing (September 2016)
- <https://www.piscltd.org.uk/inhalation-webinars/>

Keys to Implementation

- Provide clear language regarding the acceptance of NAMs
- Collaborate with international partners to facilitate global harmonization and regulatory acceptance
- Explore processes to incentivize and promote the use of NAMs
- Identify appropriate metrics for prioritizing activities, monitoring progress, and measuring success



Hazard & Science Policy Council (HASPOC)

- Reduce: Waivers for developmental, reproductive, DNT, chronic/carcinogenicity toxicity
- Refine: Special protocol studies instead of standard guideline protocols (e.g., shorter duration, fewer animals, single gender, etc)
- Refine: Pharmacokinetic studies in lieu of toxicity study
- In FY'16, waivers were granted for 153 of 180 requests resulting in savings of about 44,000 animals and over \$16 million in the cost of conducting the studies.
- In FY'17, waivers were granted for 70 of 78 requests resulting in savings of about 41,000 animals and approximately \$10.4 million in the cost of conducting the studies.

EPA OPP Waiver Evaluations

December, 2011 to April, 2018

Type of Study	Waivers Granted	Required Studies	Requests
Inhalation	229	65	294
Neurotoxicity	303	24	327
Dermal	55	8	63
Developmental	42	7	49
DNT	17	2	19
Subchronic Dog	13	3	16
Reproductive	32	6	38
Immunotoxicity	212	17	229
Chronic/ Carcinogenicity	26	2	28
Subchronic Rat	13	3	16
Total	942	137	1079

Potential elimination of ~ 2600 animals/yr./facility



United States Department of Agriculture

2018: Cryopreservation of Virulent Serogroups

Cryopreserved Serogroups

CVB has made available virulent serogroups *L. canicola*, *L. pomona*, *L. grippotyphosa*, and *L. icterohaemorrhagiae* such that the live animal is not needed to maintain strains

https://www.aphis.usda.gov/animalhealth/vetbiologics/publications/vb_reagent_catalog.pdf

Cryopreservation Protocol

CVB has created a protocol to be used by any company that wishes to cryopreserve strains on their own.

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_pros_bb

In 2013, USDA CVB Targeted a 30% Decrease in Hamster Usage

