



## Interagency Coordinating Committee on the Validation of Alternative Methods



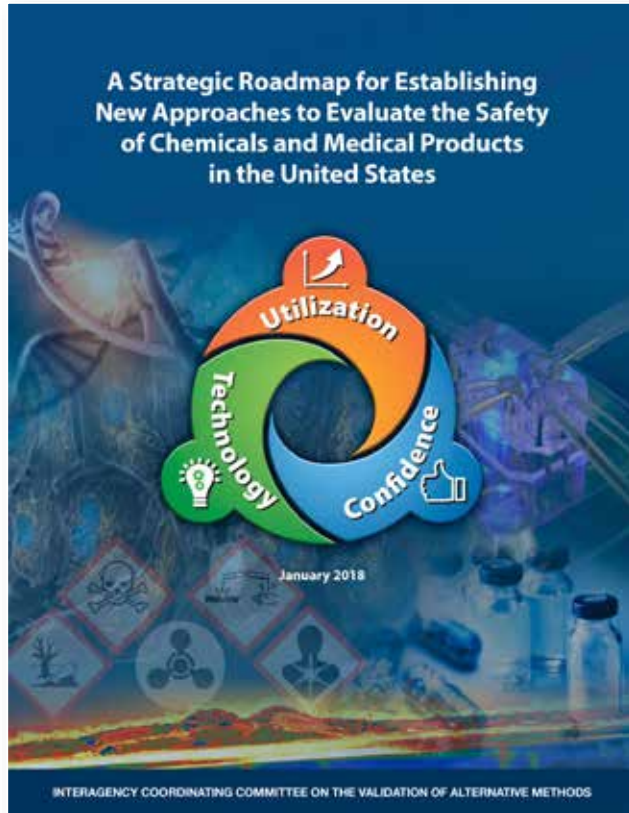
# ICCVM Update on Implementing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States

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 Institute of Standards and Technology • National Institutes of Health • National Cancer Institute • National Library of Medicine  
National Institute of Environmental Health Sciences • Occupational Safety and Health Administration



## Speakers

- Warren Casey, NICEATM
- Brian Berridge, NTP
- Suzy Fitzpatrick, FDA CFSAN
- Anna Lowit, EPA OPP
- Gino Scarano, EPA OPPT
- Emily Reinke, DoD



*U.S. agencies and stakeholders will work together to build a new framework to develop, establish confidence in, and encourage use of new approaches to toxicity testing that improve human health relevance and reduce or eliminate testing in animals.*

- Published Jan 30, 2018
- <https://ntp.niehs.nih.gov/go/natl-strategy>



**Must Start Here!**

**Help end-users guide the development of the new methods**

**Encourage the adoption of new methods**



**Use efficient and flexible approaches to establish confidence in new methods**



# Acute 6-Pack Studies

- Acute oral
- Acute dermal
- Acute inhalation
- Eye irritation
- Skin irritation
- Skin sensitization

## U.S. Strategic Roadmap

### Introduction

### Implementation

#### Acute Systemic Toxicity

#### Skin and Eye Irritation

#### Skin Sensitization

### Development

### Contributors

### References

## Strategic Roadmap: Implementation

View details of ongoing and planned activities for implementation of the Strategic Roadmap in the following areas:

- [Acute Systemic Toxicity](#)
- [Eye and Skin Irritation](#)
- [Skin Sensitization](#)

ICCVAM establishes temporary ad hoc workgroups to perform specific tasks identified by the committee as being important for the development or validation of new approach methodologies, and it is envisioned that ICCVAM workgroups will play a key role in implementing the goals of the strategic roadmap. The workgroups are chaired by representatives from agencies that use or require data from the topic of interest. The chairs are responsible for developing the group's scope and charge, which is then reviewed and approved by ICCVAM. ICCVAM member agencies and partners in the [International Cooperation on Alternative Test Methods](#) (EURL ECVAM, JaCVAM, KoCVAM, and Health Canada) are then invited to participate in the workgroup.

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<https://ntp.niehs.nih.gov/go/838279>





## U.S. Agency Requirements

Cutan Ocul Toxicol, 2018 Nov 11:1-58. doi: 10.1080/15569527.2018.1540494. [Epub ahead of print]

### United States regulatory requirements for skin and eye irritation testing.

Choksi NY<sup>1</sup>, Truax J<sup>1</sup>, Layton A<sup>2</sup>, Matheson J<sup>3</sup>, Mattie D<sup>4</sup>, Varney T<sup>5</sup>, Tao J<sup>6</sup>, Yozzo K<sup>6</sup>, McDougal AJ<sup>7</sup>, Merrill J<sup>8</sup>, Lowther D<sup>9</sup>, Barroso J<sup>10</sup>, Linke R<sup>11</sup>, Casey W<sup>12</sup>, Allen D<sup>1</sup>

Arch Toxicol, 2019 Feb;93(2):273-291. doi: 10.1007/s00204-018-2341-6. Epub 2018 Oct 30.

### Skin sensitization testing needs and data uses by US regulatory and research agencies.

Toxicol In Vitro, 2018 Apr;48:53-70. doi: 10.1016/j.tiv.2017.12.011. Epub 2017 Dec 22.

Strickland J<sup>1</sup>, Daniel AB<sup>2</sup>, Allen D<sup>2</sup>,  
Lehmann DM<sup>10</sup>, Matheson J<sup>11</sup>, Reir

### Alternative approaches for acute inhalation toxicity testing to address global regulatory and non-regulatory data requirements: An international workshop report.

Regul Toxicol Pharmacol, 2018 Jun;95:52-65. doi: 10.1016/j.yrtph.2018.03.003. Epub 2018 Mar 6.

Albourne J<sup>9</sup>, Hinderliter P<sup>10</sup>,

### International regulatory requirements for skin sensitization testing.

Daniel AB<sup>1</sup>, Strickland J, Regul Toxicol Pharmacol, 2018 Apr;94:183-196. doi: 10.1016/j.yrtph.2018.01.022. Epub 2018 Feb 3.  
Park HK<sup>11</sup>, Lee JK<sup>12</sup>, K

### Status of acute systemic toxicity testing requirements and data uses by U.S. regulatory agencies.

Strickland J<sup>1</sup>, Clippinger AJ<sup>2</sup>, Brown J<sup>3</sup>, Allen D<sup>4</sup>, Jacobs A<sup>5</sup>, Matheson J<sup>6</sup>, Lowit A<sup>7</sup>, Reinke EN<sup>8</sup>, Johnson MS<sup>9</sup>, Quinn MJ Jr<sup>10</sup>, Mattie D<sup>11</sup>, Fitzpatrick SC<sup>12</sup>, Ahir S<sup>13</sup>, Kleinstreuer N<sup>14</sup>, Casey W<sup>15</sup>.



# New Approaches for Establishing Confidence



## From

- Centralized (“VAMs”)
- Discrete (Validated / Not)
- Stand Alone (1:1)
- Generic Applicability: regulatory context and chemical space (one size fits all)

## Towards

- Decentralized (End Users)
- Evolving Confidence
- Integrative (Many:1, Many:?)
- Customer-Focused (Fit for *Specific Purpose*)



*Toxicol In Vitro*, 2018 Aug;50:43

## Round robin study of an in vitro skin irritation test with plant extracts.

De Jong WH<sup>1</sup>, Hoffmann S<sup>2</sup>,  
M<sup>10</sup>, Schatz T<sup>11</sup>, Skoog S<sup>12</sup>,  
Meloni M<sup>19</sup>, Julius C<sup>20</sup>, Briote  
Christiano N<sup>23</sup>, Rollins TS<sup>3</sup>, C

Contents lists available at [ScienceDirect](#)

- <sup>a</sup> National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
- <sup>b</sup> Seh consulting + services, Paderborn, Germany
- <sup>c</sup> Nelson Laboratories, Inc., Salt Lake City, UT, USA
- <sup>d</sup> MatTek In Vitro Life Science Laboratories, Bratislava, Slovakia
- <sup>e</sup> EPISKIN, Lyon, France
- <sup>f</sup> National Institute of Health Sciences (NIHS), Division of Medical Devices, Tokyo, Japan
- <sup>g</sup> Arthrex, Inc., Naples, FL, USA<sup>1</sup>
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- <sup>j</sup> MatTek Corporation, Ashland, MA, USA
- <sup>k</sup> American Preclinical Services LLC, Minneapolis, MN, USA
- <sup>1</sup> US Food and Drug Administration, Center for Devices and Radiological Health, Silver Spring, MD, USA
- <sup>m</sup> WuXi AppTec, St Paul, MN, USA
- <sup>n</sup> Becton Dickinson, Research Triangle Park, NC, USA
- <sup>o</sup> Eurofins Biolab Srl, Vimodrone, Milan, Italy
- <sup>p</sup> SP Technical Research Institute of Sweden, Borås, Sweden
- <sup>q</sup> Yonsei University, College of Dentistry, Seoul, South Korea
- <sup>r</sup> Eurofins Biopharma, Planegg, Munich, Germany
- <sup>s</sup> VitroScreen, Milan, Italy
- <sup>t</sup> Envigo CRS GmbH, Rossdorf, Germany
- <sup>u</sup> NAMSA, Chasse sur Rhône, France
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- <sup>w</sup> Medtronic, plc, Minneapolis, MN, USA

# Comprehensive In Vitro Proarrhythmia Assay (CiPA)

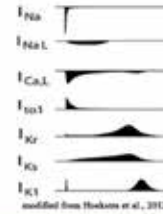


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## CiPA Initiative

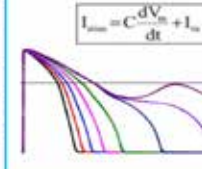
The objective of the CiPA initiative is to facilitate the adoption of a new paradigm for assessment of clinical potential of TdP that is not measured exclusively by potency of hERG block and not as all by QT prolongation.

### Drug Effects on Multiple Human Cardiac Currents

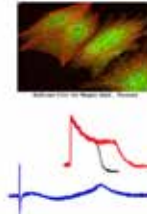


modified from Hinkins et al., 2013

### In Silico Reconstruction Human Ventricular Cellular Electrophysiology



### In Vitro Effects Human Stem-Cell Derived Ventricular Myocytes



### Clinical Evaluation Unanticipated EP Effects



[US FDA](#), [HESI](#), [CSRC](#), [SPS](#), [EMA](#), [Health Canada](#), [Japan](#)  
[NIHS](#), [PMDA](#)

The objective of the CiPA initiative is to facilitate the **adoption of a new paradigm** for assessment of cardiotoxicity. The new CiPA paradigm will be driven by a suite of mechanistically based **in vitro assays** coupled to **in silico reconstructions** of cellular cardiac electrophysiologic activity



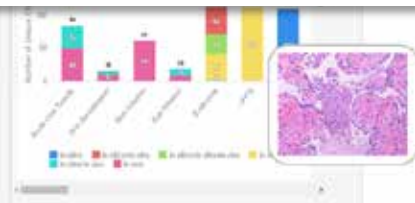
# Future Directions



## Web Tool Demos

Visit the NTP booth at ToxExpo (#3428) for an overview and hands-on tutorial on the Open Structure-Activity/Property Relationship App (OPERA) and the Integrated Chemical Environment (ICE).

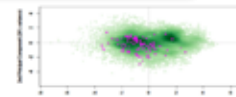
- **Monday, March 11** – 2:30-4:00 p.m.
- **Tuesday, March 12** – 2:00-4:00 p.m.
- **Wednesday, March 13** – 10:00 a.m.-noon



Run workflows

In vitro to in vivo  
extrapolation

And more coming spring 2019...



Chemical space  
characterization

other  
rces

ng

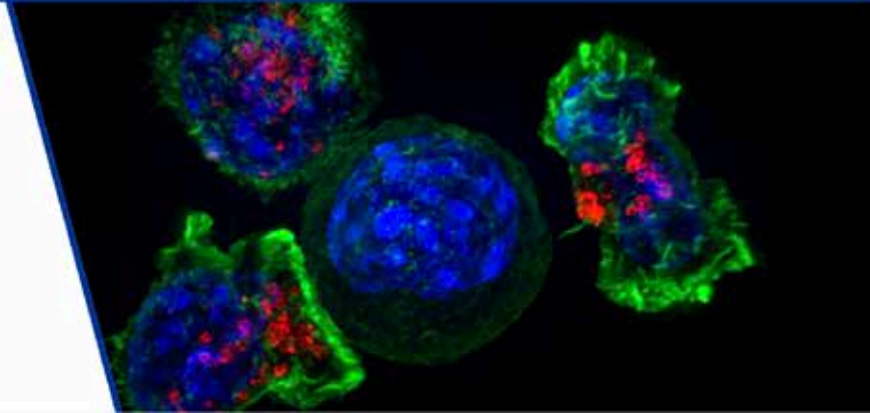
## Biomedical Data Translator

The Translator program is funded through the [Cures Acceleration Network](#) (CAN). CAN is designed to advance the development of high-need cures and reduce significant barriers between research discovery and clinical trials. [Learn more about the Biomedical Data Translator program.](#)



### Deconstructing the Translational Tower of Babel

Find out how NCATS' Biomedical Data Translator program aims to help bridge informatics gaps in an editorial by NCATS leadership in Clinical and Translational Science. [▶](#)



Collaboration between academic and private-sector partners to create a comprehensive, relational, N-dimensional “data translator” that integrates multiple types of existing data sources.

## We are building a research program of 1,000,000+ people

The mission of the *All of Us* Research Program is to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care for all of us.

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environment

lifestyle

biology

Research focuses on the intersection of 3 factors





## NICEATM / ILS Support Staff



RTP, NC



NIH

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# Questions?