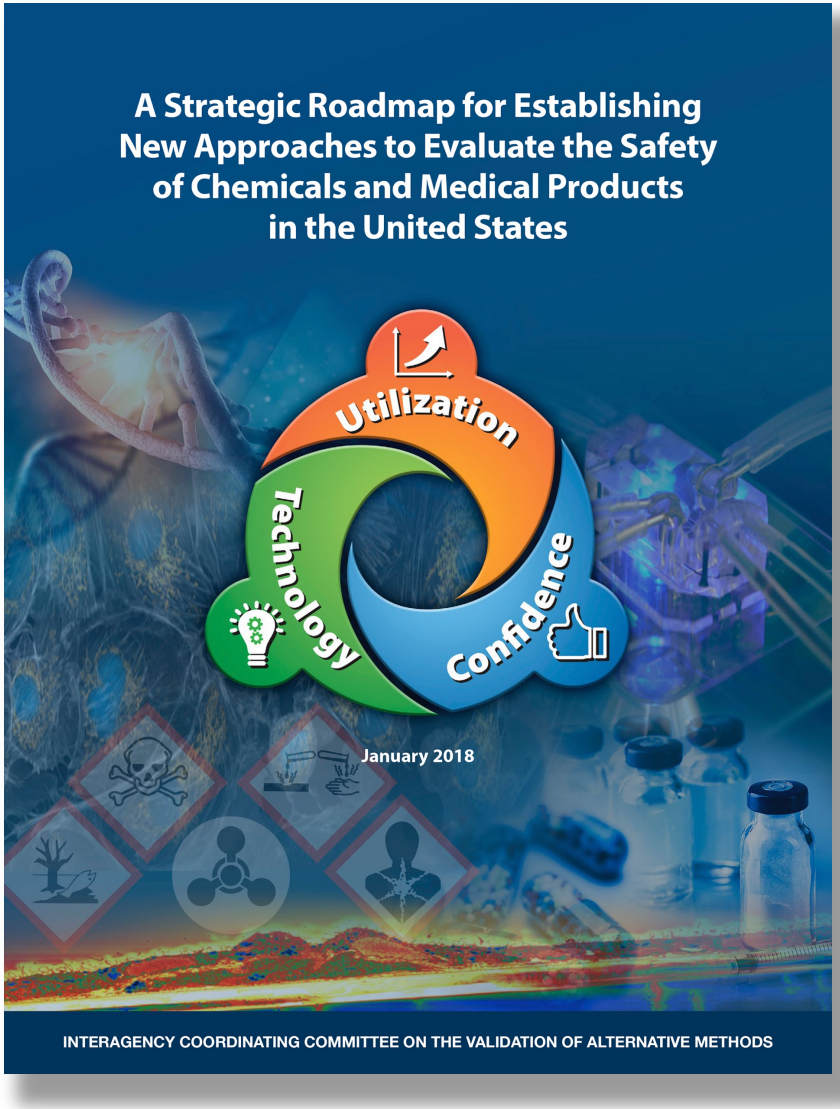
ICCVAM Roadmap and Implementation Plan: Progress Update

Anna Lowit, U.S. EPA

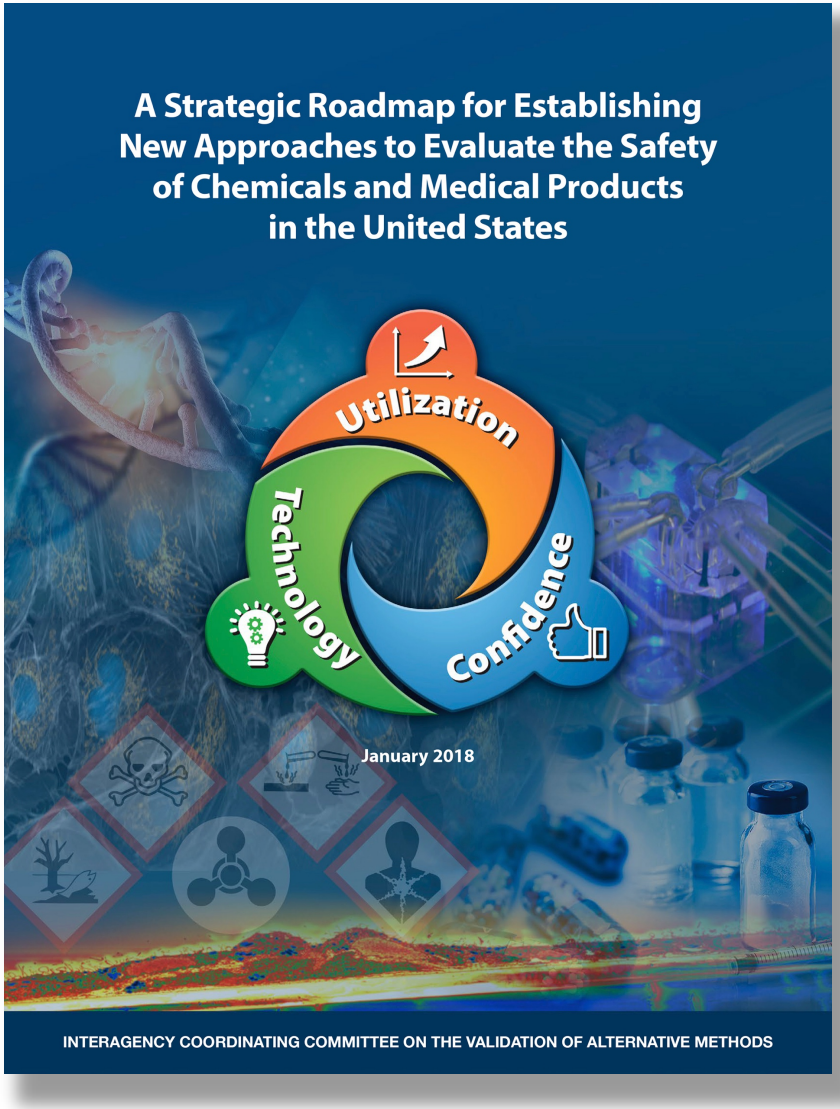
ICCVAM Public Forum
May 23, 2019

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



- **Connect end users with the developers of alternative methods**
- **Establish new validation approaches that are more flexible and efficient**
- **Ensure adoption and use of new methods by both regulators and industry**

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



- Protecting public health and Improving human relevance are key drivers
- Guided by the priorities of agencies
- Paired with implementation plans will be tracked and publically reported

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


A Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States
Utilization
Technology
Confidence
January 2018
INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS


Um roteiro estratégico para o estabelecimento de novas abordagens de avaliação da segurança de produtos químicos e de produtos hospitalares nos Estados Unidos
Utilization
Technology
Confidence
Janeiro de 2018
COMITÊ DE COORDENAÇÃO INTERINSTITUCIONAL PARA A VALIDAÇÃO DE MÉTODOS ALTERNATIVOS
(INTERAGENCY COORDINATING COMMITTEE ON THE VALIDATION OF ALTERNATIVE METHODS)


为评估美国化学品及医疗产品安全性建立新方案的战略发展蓝图
Utilization
Technology
Confidence
2018年1月
替代方法验证跨部门协调委员会

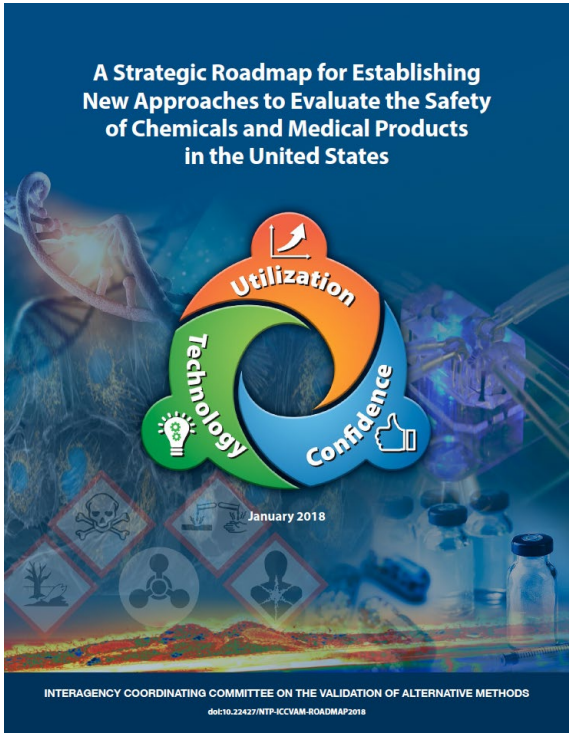

Una guía estratégica para establecer nuevos enfoques para evaluar la seguridad de productos químicos y médicos en los Estados Unidos
Utilization
Technology
Confidence
Enero de 2018
COMITÉ DE COORDINACIÓN INTERINSTITUCIONAL PARA LA VALIDACIÓN DE MÉTODOS ALTERNATIVOS


미국 내 화학 제품 및 의약품 안전 평가를 위한 새로운 접근법 확립을 위한 전략적 로드맵
Utilization
Technology
Confidence
2018년 1월
대체 시험법 검증에 관한 기관간 조정위원회


米国の化学薬品と医薬品の安全性評価に対する新しいアプローチを確立するための戦略的ロードマップ
Utilization
Technology
Confidence
2018年1月
代替法の検証に関する機関内調整委員会

Implementation Plan Outline

- Coordinate activities via ICCVAM Workgroups
- Draft a scoping document to identify U.S. agency requirements, needs, and decision contexts
- Coordinate efforts with stakeholders
- Identify, acquire, and curate high quality data from reference test methods
- Identify and evaluate non-animal alternative approaches
- Gain regulatory acceptance and facilitate use of non-animal approaches



Implementation Plan:

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ICCVAM Workgroups

- Acute Systemic Toxicity
  - Oral
  - Dermal
  - Inhalation
- Eye and Skin Irritation
- Skin Sensitization
- Developmental and Reproductive Toxicity
- Ecotoxicology
- Nanomaterials
- IVIVE
- Read Across

Implementation Plan:

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Regulatory Toxicology and Pharmacology 94 (2018) 183–196
Contents lists available at ScienceDirect
Regulatory Toxicology and Pharmacology
journal homepage: www.elsevier.com/locate/yrtph

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

Judy Strickland[a,*], Amy J. Clippinger[b], Jeffrey Brown[b], David Allen[a], Abigail Jacobs[c,1], Joanna Matheson[d], Anna Lowit[e], Emily N. Reinke[f], Mark S. Johnson[f], Michael J. Quinn Jr.[f], David Mattie[g], Suzanne C. Fitzpatrick[h], Surender Ahir[i], Nicole Kleinstreuer[j], Warren Casey[j]

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[c] Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), Whi
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[d] U.S. Consumer Product Safety Commission, 5 Research Place, Rockville, MD 20850, USA
[e] Office of Pesticide Programs, U.S. Environmental Protection Agency, 1200 Pennsylvania A
[f] U.S. Army Public Health Center, 5158 Blackhawk Rd., Aberdeen Proving Ground, MD 210
[g] U.S. Air Force, Air Force Research Laboratory, AFRL/711 HPW RHDJ, 711 Human Perfo
[h] Center for Food Safety and Applied Nutrition, FDA, Harvey W. Wiley Building, 5100 Pain
[i] U.S. Occupational Safety and Health Administration, 200 Constitution Ave. NW, Washingt
[j] National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicolog
12233, Research Triangle Park, NC 27709, USA

ARTICLE INFO

Keywords:
Acute systemic toxicity
Alternative approaches
Non-animal methods
Regulatory requirements
LD_{50}
LC_{50}
In vitro
In silico

ABSTRACT

Acute systemic toxicity da
fication and labeling and
implementation of non-an
temic toxicity information
for six U.S. agencies (C
Transportation, Environm
Health Administration) an
or reduce animal use. Und
starting point for future
inform the development o
potential hazards associat
Toxicity Workgroup of th
(ICCVAM), U.S. agencies,
strategy.

CUTANEOUS AND OCULAR TOXICOLOGY
2019, VOL. 38, NO. 2, 141–155
https://doi.org/10.1080/15569527.2018.1540494
Taylor & Francis
Taylor & Francis Group
Check for updates

REVIEW ARTICLE

United States regulatory requirements for skin and eye irritation testing

Neepa Y. Choksi[a], James Truax[a], Adrienne Layton[b], Joanna Matheson[c], David Mattie[d], Timothy Varney[e], Jenny Tao[f], Krystle Yozzo[f], Andrew J. McDougal[g], Jill Merrill[h], Donnie Lowther[i], Joao Barroso[j], Brenda Linke[k], Warren Casey[l] and David Allen[a]

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hemical regulation authorities
ss risks for exposure to skin-
and interest in implementing
f non-animal skin- and eye-
non-animal replacements for
data at U.S. regulatory and

J.S. Interagency Coordinating
or skin and eye irritation test-
ation data required by each
classification, or risk assess-
e acceptable. Information on
ollected.
der non-animal or alternative
ncy in designing their testing
or local skin and eye irrita-

hods, a dialog on the confi-
ent must be undertaken at

ARTICLE HISTORY
Received 23 August 2018
Revised 16 October 2018
Accepted 18 October 2018

KEYWORDS
Eye irritation testing; skin irritation testing; alternative approaches; non-animal methods; regulatory requirements; corrosive

Archives of Toxicology (2019) 93:273–291
https://doi.org/10.1007/s00204-018-2341-6

REGULATORY TOXICOLOGY

CrossMark

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

Judy Strickland[1] · Amber B. Daniel[1] · David Allen[1] · Cecilia Aguila[2] · Surender Ahir[3] · Simona Bancos[4] · Evisabel Craig[5] · Dori Germolec[6] · Chandramallika Ghosh[4] · Naomi L. Hudson[7] · Abigail Jacobs[8] · David M. Lehmann[9] · Joanna Matheson[10] · Emily N. Reinke[11] · Nakissa Sadrieh[12] · Stanislav Vukmanovic[12] · Nicole Kleinstreuer[13]

Received: 1 August 2018 / Accepted: 23 October 2018 / Published online: 30 October 2018

Abstract
United States regulatory and research agencies may rely upon skin sensitization test data to assess the sensitization hazards associated with dermal exposure to chemicals and products. These data are evaluated to ensure that such substances will not cause unreasonable adverse effects to human health when used appropriately. The US Consumer Product Safety Commission, the US Environmental Protection Agency, the US Food and Drug Administration, the Occupational Safety and Health Administration, the National Institute for Occupational Safety and Health, and the US Department of Defense are member agencies of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). ICCVAM seeks to identify opportunities for the use of non-animal replacements to satisfy these testing needs and requirements. This review identifies the standards, test guidelines, or guidance documents that are applicable to satisfy each of these agency's needs; the current use of animal testing and flexibility for using alternative methodologies; information needed from alternative tests to fulfill the needs for skin sensitization data; and whether data from non-animal alternative approaches are accepted by these US federal agencies.

Keywords Skin sensitization testing · Alternative approaches · Non-animal methods · Regulatory requirements

- Identifies requirements, needs, and decision contexts data for each endpoint

ICCVAM Agency Needs and Decision Contexts

- ✅ **Acute Systemic Oral, PMID: 29408321**
- ✅ **Acute Systemic Dermal, PMID: 29408321**
- ✅ **Acute Systemic Inhalation, PMID: 29408321**
- ✅ **Eye Irritation, PMID: 30418044**
- ✅ **Skin Irritation, PMID: 30418044**
- ✅ **Skin Sensitization, PMID: 30377734 (U.S.) / 29518484 (Int.)**
- ✅ **Read Across, just accepted (no PMID yet)**

PMID – PubMed ID

ICCVAM Agency Needs and Decision Contexts

- ✅ **Acute Systemic Oral, PMID: 29408321**
- ✅ **Acute Systemic Dermal, PMID: 29408321**
- ✅ **Acute Systemic Inhalation, PMID: 29408321**
- ✅ **Eye Irritation, PMID: 30418044**
- ✅ **Skin Irritation, PMID: 30418044**
- ✅ **Skin Sensitization, PMID: 30377734 (U.S.) / 29518484 (Int.)**
- ✅ **Read Across, just accepted (no PMID yet)**

✅ Completed for all “6-Pack” tests!

PMID – PubMed ID

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Predictive Models for Acute Oral Systemic Toxicity

- April 2018 workshop
- Workshop attendees in-person: 89; webcast: 215
- **35** Participants/Groups from around the globe representing academia, industry, and government contributed
- **139** Models total

Computational Toxicology 8 (2018) 21–24

Contents lists available at ScienceDirect

Computational Toxicology

journal homepage: www.elsevier.com/locate/comtox

Predictive models for acute oral systemic toxicity: A workshop to bridge the gap from research to regulation

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ARTICLE INFO

Keywords:
QSAR
Read-across
Acute oral toxicity
ICCVAM
Workshop

ABSTRACT

In early 2018, the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) published the "Strategic Roadmap for Establishing New Approaches to Evaluate the Safety of Chemicals and Medical Products in the United States" [1]. Cross-agency federal workgroups have been established to implement this roadmap for various toxicological testing endpoints, with an initial focus on acute toxicity testing. The ICCVAM acute toxicity workgroup (ATWG) helped organize a global collaboration to build predictive *in silico* models for acute oral systemic toxicity, based on a large dataset of rodent studies and targeted towards regulatory needs identified across federal agencies. Thirty-two international groups across government, industry, and academia participated in the project, culminating in a workshop in April 2018 held at the National Institutes of Health (NIH). At the workshop, computational modelers and regulatory decision makers met to discuss the feasibility of using predictive model outputs for regulatory use in lieu of acute oral systemic toxicity testing. The models were combined to yield consensus predictions which demonstrated excellent performance when compared to the animal data, and workshop outcomes and follow-up activities to make these tools available and put them into practice are discussed here.

Review of Mechanisms of Acute Inhalation Toxicity, Dosimetry, and Non-Animal Methods

Toxicology in Vitro 52 (2018) 131–145

Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

Review

Pathway-based predictive approaches for non-animal assessment of acute inhalation toxicity

Amy J. Clippinger[a,*], David Allen[b], Holger Behrsing[c], Kelly A. BéruBé[d], Michael B. Bolger[e], Warren Casey[f], Michael DeLorme[g], Marianna Gaça[h], Sean C. Gehen[i], Kyle Glover[j], Patrick Hayden[k], Paul Hinderliter[l], Jon A. Hotchkiss[m], Anita Iskandar[n], Brian Keyser[o], Karsta Luettich[n], Lan Ma-Hock[p], Anna G. Maione[k], Patrudu Makena[o], Jodie Melbourne[a], Lawrence Milchak[g], Sheung P. Ng[q], Alicia Paini[r], Kathryn Page[s], Grace Patlewicz[t], Pilar Prieto[r], Hans Raabe[c], Emily N. Reinke[u], Clive Roper[v], Jane Rose[w], Monita Sharma[a], Wayne Spoo[o], Peter S. Thorne[x], Daniel M. Wilson[m], Annie M. Jarabek[y]

Review of Mechanisms of Acute Inhalation Toxicity, Dosimetry, and Non-Animal Methods

Contributing Organizations

- NIEHS, NICEATM
- U.S. Environmental Protection Agency
- U.S. Army Public Health Center
- U.S. Defense Threat Reduction Agency
- European Commission, Joint Research Centre (JRC)
- RAI Services Company
- Charles River
- Procter & Gamble Co
- The Clorox Company
- BASF
- DuPont Haskell Global Center for Health Sciences
- Institute for In Vitro Sciences
- PETA International Science Consortium
- Cardiff School of Biosciences
- University of Iowa College of Public Health
- Integrated Laboratory Systems
- Simulations Plus, Inc
- 3M
- British American Tobacco
- Dow AgroSciences
- MatTek Corporation
- Syngenta
- The Dow Chemical Company
- Philip Morris International
- RAI Services Company

Hans Raabe[c], Emily N. Reinke[u], Clive Roper[v], Jane Rose[w], Monita Sharma[a], Wayne Spoo[o], Peter S.

Honorable Mention winner, Best Paper of 2018, Society of Toxicology Biological Modeling Specialty Section

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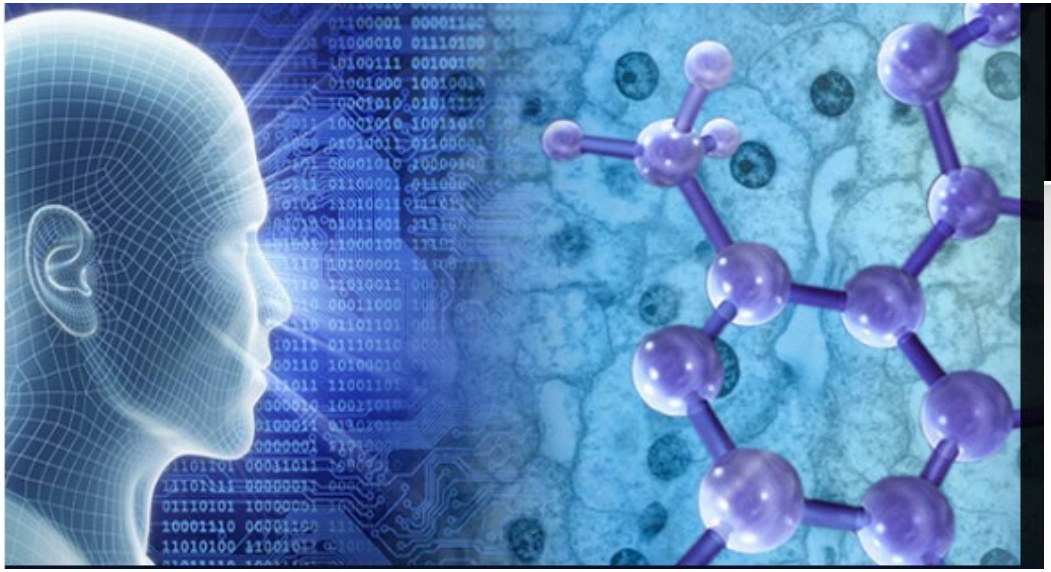
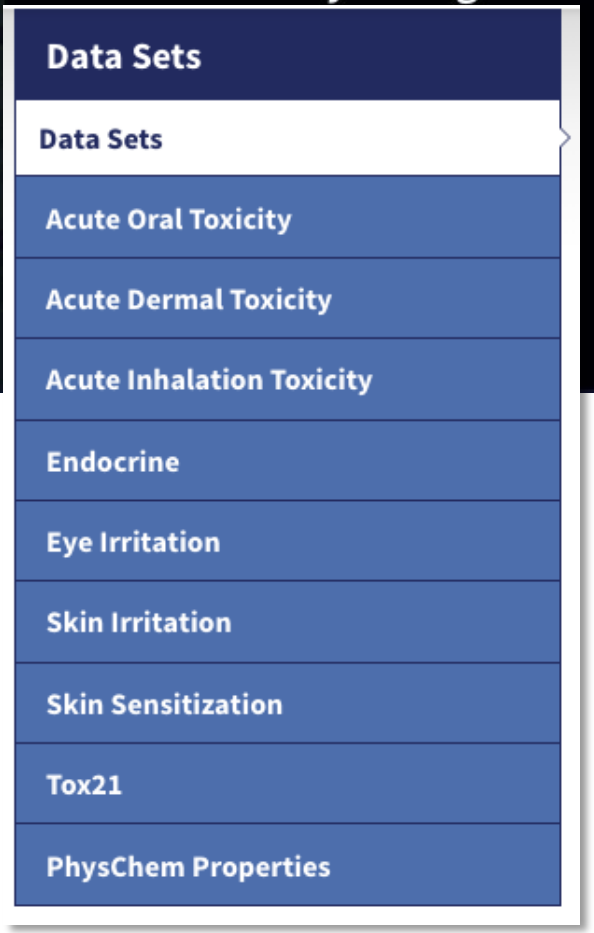
Integrated Chemical Environment https://ice.ntp.niehs.nih.gov/



ICE provides data to support development of new approaches for chemical safety testing.



Recently Added:

All Tox 21 Data
Eye Irritation-Corrosion
ER In Vitro
Uterotrophic
AR In Vitro
Hershberger

Details to be presented under NICEATM update

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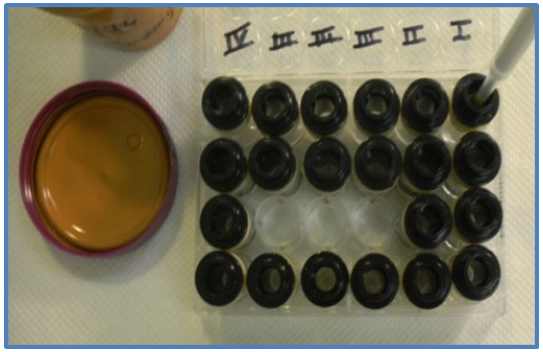
EASA Validation Study Objectives

- To characterize the usefulness and limitations of the **E**lectrophilic **A**llergen **S**creening **A**ssay (**EASA**), to classify the allergic contact dermatitis hazard of products and chemicals
  - Optimize and standardize the test method protocol
  - Assess intra- and inter-laboratory reproducibility
  - Assess accuracy for classification of hazard

- Study update and timeline to be presented later today by NIST.

Interlaboratory Validation Study: OptiSafe Method

Phase	Activities
Pre-Study Phase	• Formation of VMT - composed of ICCVAM agency scientists and international representatives • Selection of naïve laboratories • Finalization of documents, reporting forms, and performance criteria
Phase I	• Qualification and training of naïve laboratories • Testing of all practice chemicals by lead and naïve laboratories
Phase II	• Testing of 30 chemicals by lead and naïve laboratories
Phase III	• Testing of 60 chemicals by lead laboratory
Reporting Phase	• Preparation of validation report



- ICCVAM ODIWG members serve as the Validation Management Team
- **Report finalized** – manuscript in preparation

Progress on Implementation can be followed here:

Strategic Roadmap: Implementation

SHARE THIS:
https://ntp.niehs.nih.gov/go/838279

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.

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

Thank you!

Questions?