UNITED STATES ICCVAM Advancing Alternatives to Animal Testing

Interagency Coordinating Committee on the Validation of Alternative Methods

20 YEARS

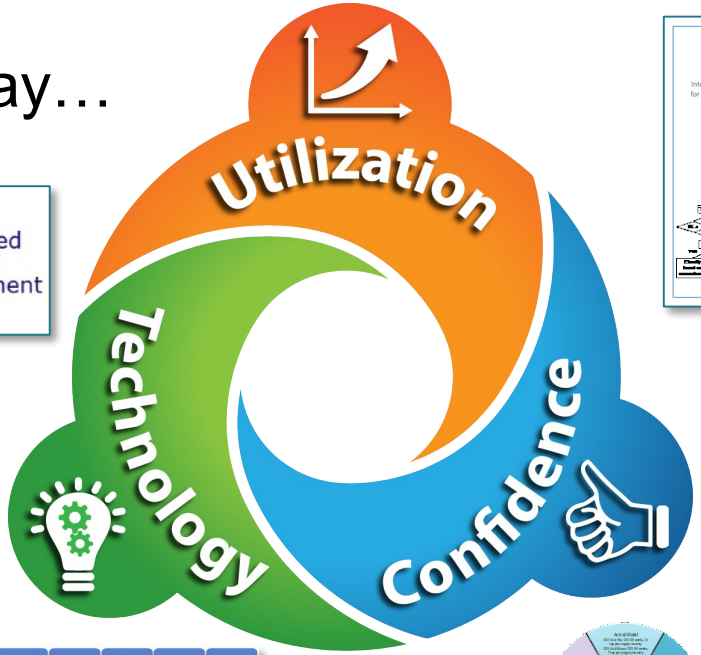
Implementing the Strategic Roadmap

SACATM Meeting
September 2-3, 2020

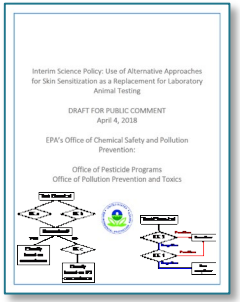
Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Institute of Standards and Technology • National Library of Medicine • Occupational Safety and Health Administration

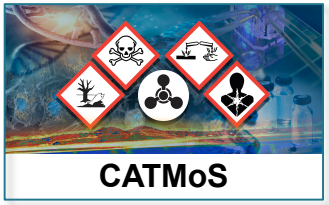
Implementation of the Roadmap

Where we are today…

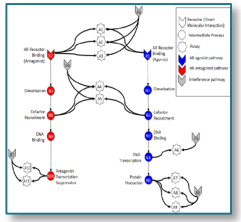


Integrated Chemical Environment





CATMoS



Ongoing NICEATM Efforts

- Integrated Chemical Environment
- OPERA (QSAR/QSPR)
- Data curation
- Variability of in vivo data
- Acute Systemic Toxicity
- Dermal absorption
- Eye and skin irritation
- SEAZIT
- Skin sensitization
- Acute Fish Retrospective
- Carcinogenesis
- Cardiovascular toxicity
- Animal-free affinity reagents

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 Plans

- Acute systemic toxicity
  https://ntp.niehs.nih.gov/go/roadmap-acutetox
- Skin and eye irritation
  https://ntp.niehs.nih.gov/go/roadmap-irrit
- Skin sensitization
  https://ntp.niehs.nih.gov/go/roadmap-sensit

Interagency Coordinating Committee on the Validation of Alternative Methods

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

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REGULATORY TOXICOLOGY

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

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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

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REVIEW ARTICLE

United States regulatory requirements for skin and eye irritation testing

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...est data are required or considered by chemical regulation authorities ...product hazard labelling and/or to assess risks for exposure to skin- ...combination of animal welfare concerns and interest in implementing ...levance has led to the development of non-animal skin- and eye- ...ty opportunities for regulatory uses of non-animal replacements for ...needs and uses for these types of test data at U.S. regulatory and ...rified.
...y and non-regulatory testing needs of U.S. Interagency Coordinating ...lternative Methods (ICCVAM) agencies for skin and eye irritation test- ...ncludes the type of skin and eye irritation data required by each ...on context: hazard classification, potency classification, or risk assess- ...hether alternative or non-animal tests are acceptable. Information on ...om non-animal test methods also was collected.
... U.S. agencies is the willingness to consider non-animal or alternative ...raged to consult with the relevant agency in designing their testing ...d acceptance of alternative methods for local skin and eye irrita-
...plementation of alternative testing methods, a dialog on the confi- ...otect public health and the environment must be undertaken at

ARTICLE HISTORY
Received 23 August 2018
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KEYWORDS
Eye irritation testing; skin irritation testing; alternative approaches; non-animal methods; regulatory requirements; corrosive

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

Workshop

SHARE THIS:
https://ntp.niehs.nih.gov/go/atwksp-2019

Mind the Gaps: Prioritizing Activities to Meet Regulatory Needs for Acute Systemic Lethality

October 30-31, 2019
Porter Neuroscience Research Center
National Institutes of Health
Bethesda, Maryland, USA

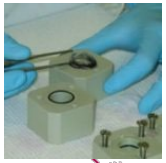
- Co-organized by PCRM and NICEATM
- Participants included stakeholders from government, industry, NGOs
- Discussion topics included:
  - Estimating the LD50 of a chemical mixture/formulated product
  - Identifying gaps where model (or assay) development or optimization is needed
  - Pinpointing the types of mechanistic information that would be useful
  - Establishing the feasibility of using artificial intelligence in model development

Acute 6-Pack Alternatives

Dermal lethality	• Waiver guidance available
Oral lethality	• In silico approaches for single chemicals; additivity for formulations under consideration
Inhalation lethality	• 3D models being evaluated; LC50 database for model development being built
Eye irritation	• NAMs for Cat I and/or Cat IV? (TG 437, 438, 460, 491, 492, 494); Prospective testing ongoing
Skin irritation	• NAMs for Cat I or Cat IV? (TG 430, 431, 435, 439); Prospective testing ongoing
Skin sensitization	• Science policy and draft risk assessment using DAs

Prospective Testing: Agchems and Eye Irritation

syngenta
CORTEVA agriscience
BASF We create chemistry
FMC
BAYER

BCOP


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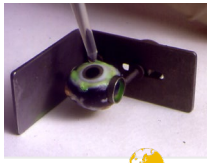
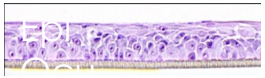
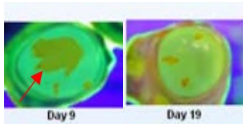


EpiOcular


NRR

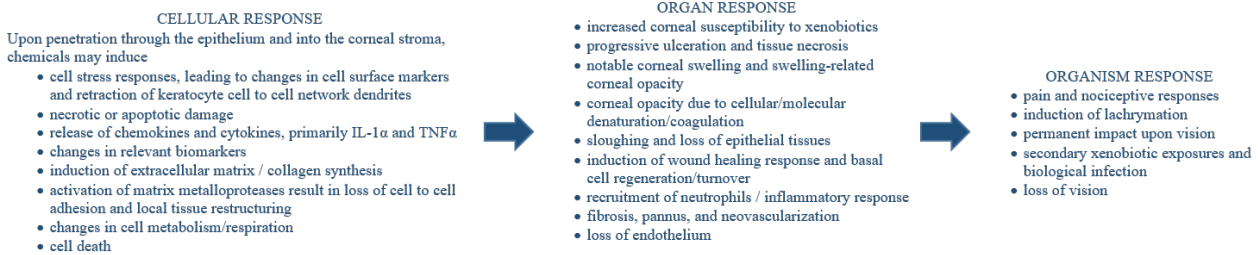

PorCORA


- N=16 formulations (donated by companies) tested to date; No single test method correctly identified all 16 relative to their in vivo classifications.
- Combining results of multiple tests in an integrated approach may be useful in correct classification
- Results based on binary classification also explored
- Co-organized by NICEATM and the PETA International Science Consortium, with stakeholders from ICCVAM, EURL ECVAM, PMRA, and industry

Development of a Human-Relevant Defined Approach to Assess Eye Corrosion/Irritation Potential

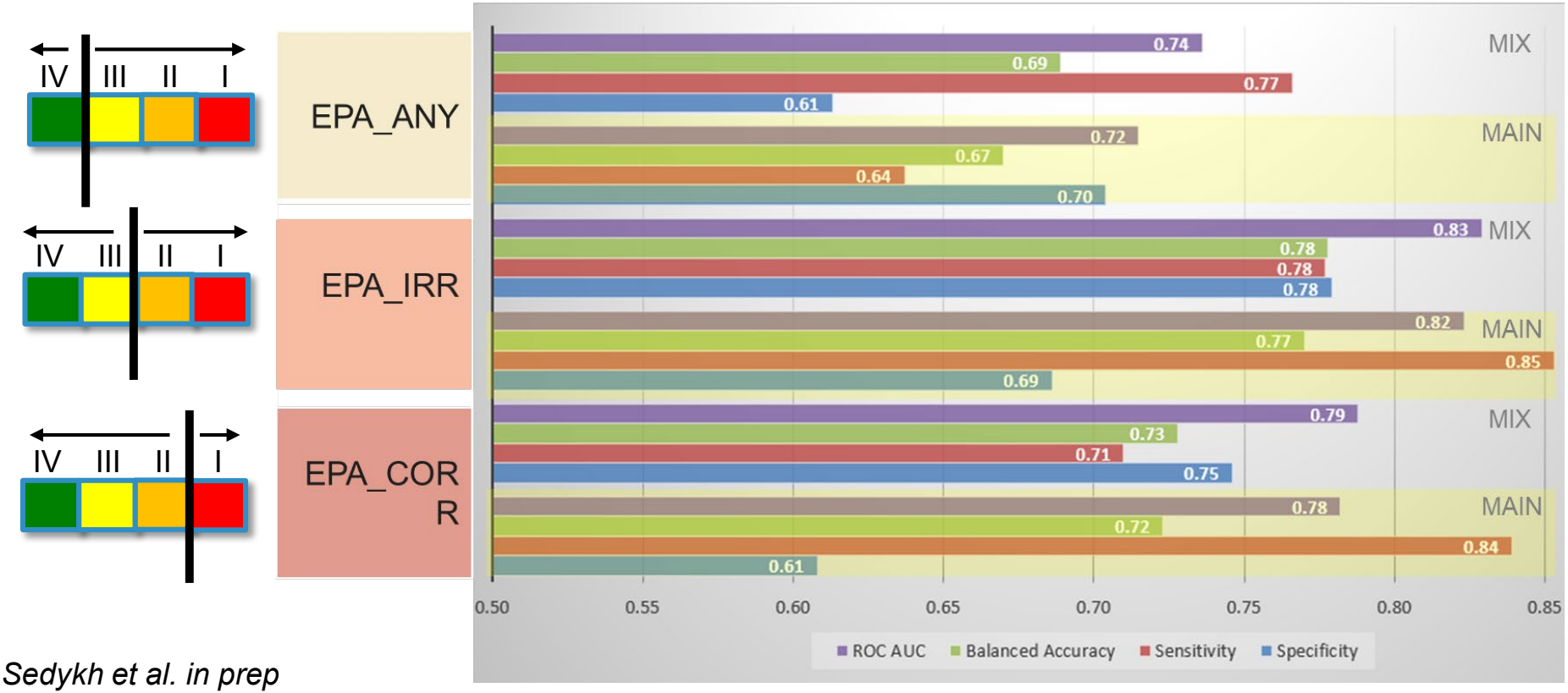
- Collaboration of Stakeholders EPA, NICEATM, PETA-ISC, CROs, Industry
- Reviewing available in vivo, in vitro and ex vivo test methods with respect to their relevance to human ocular anatomy, anticipated exposure scenarios, and the mechanisms of eye irritation/corrosion in humans.
- Compare/contrast to the human eye to identify features that are human relevant and to identify how they can be improved upon to increase their human relevance.
- Strengths and limitations of each method considered to assess which existing approaches are as good as or better than the currently used in vivo approach.

Ex: Damage into the corneal stroma



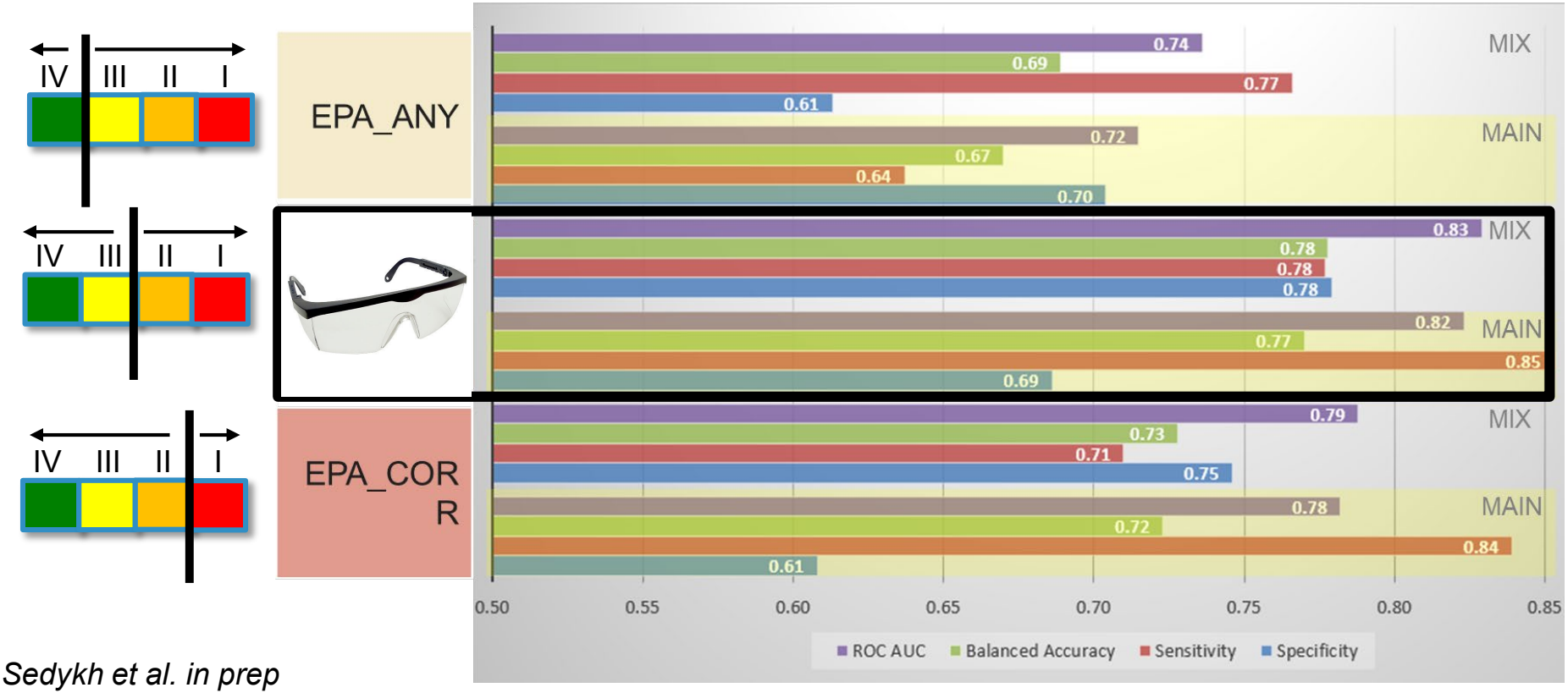
Clippinger et al. in prep

Ocular QSAR Performance



Sedykh et al. in prep

Ocular QSAR Performance



Sedykh et al. in prep

Skin Irritation: Private-Public Partnership

- Optimization of 3D skin model for testing agrochemicals and antimicrobial cleaning products (AMCPs)
- Companies donated agrochemical formulations and AMCPs
- Protocol optimization studies conducted at IIVS
- Regular stakeholder teleconferences to discuss updates, data needs, etc.
  - PISC, PCRM
  - EPA and NTP
  - Industry

Skin Data

Company	# Formulations
Church & Dwight	1
Clorox	9
Colgate	1
Ecolab	36
P&G	8
SCJ	10
Total	**65**

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