Ocular and Dermal Irritation Implementation Plan

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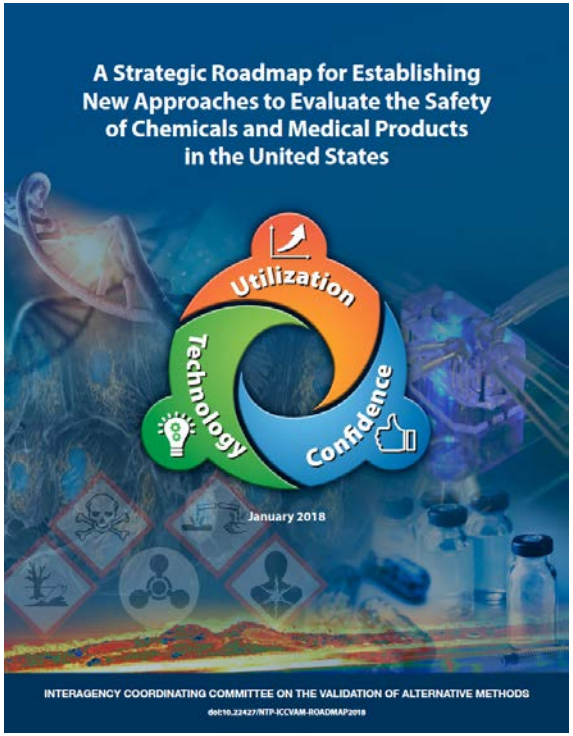
Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute 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

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



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Current Ocular and Dermal Irritation Workgroup Roster

- Adrienne Layton (CPSC)
- Joanna Matheson (CPSC)
- David Mattie (DOD)
- Timothy Varney (DOD)
- Evisabel Craig (EPA, OPP)
- Krystle Yozzo (EPA, OPP)
- Jenny Tao (EPA, OPP)
- Todd Stedeford (EPA, OPPT)
- Jill Merrill (FDA, CDER, WG Chair)
- Andrew J. McDougal (FDA, CDER)
- Donnie Lowther (FDA, CFSAN)
- Warren Casey (NIEHS)
- Elizabeth Maull (NIEHS)

ICATM Liaison Members

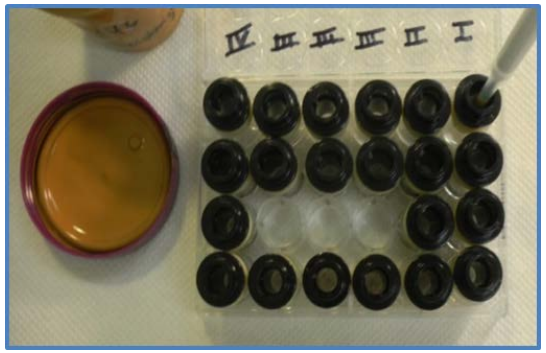
- João Barroso (EURL ECVAM)
- Yavinder Bhuller (Health Canada)
- Brenda Linke (Health Canada)

NICEATM Support Staff (ILS)

- Amber Daniel
- Neepa Choksi
- David Allen

Validation Study: OptiSafe Method

- Manufactured kit for ocular irritant/non-irritant classification
- Irritation prediction based on measured molecular damage
- 2-Phase Validation Study
  - Bottom-up approach (non-irritants vs all irritant classes)
  - Phase I: Initial qualification of naïve labs and protocol refinement
  - Phase II: Testing of 30 chemicals by all 3 labs, additional 60 tested by main lab
- Testing complete – finalizing report
- ICCVAM ODIWG members make up the VMT



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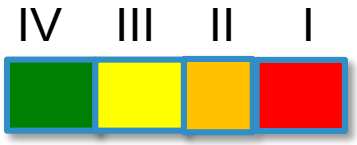
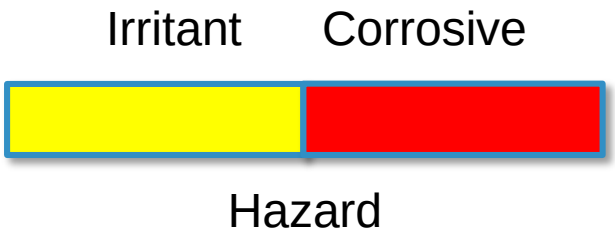
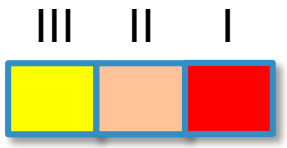
Eye/Skin Irritation and Corrosion: U.S. Statutes and Regulations

US Statute/Regulations	Agency
Federal Hazardous Substances Act (FHSA) (1960): 16 CFR 1500.3: **Consumer Products** Poison Prevention Packaging Act (1970): 16 CFR 1700: **Hazardous Household Substances**	CPSC
Federal Hazardous Material Transportation Act (1975): 49 CFR 173.132, 49 CFR 173.137: **Transported Substances**	DOT
Federal Insecticide, Fungicide, and Rodenticide Act (U.S.C. Title 7, Chapter 6): 40 CFR 156, 40 CFR 158.500, 40 CFR 158.2140, 40 CFR 158.2230, 40 CFR 159.165: **Pesticides**	EPA
Toxic Substances Control Act (TSCA; 1976): 40 CFR 720.50: **New or Imported Chemicals**	EPA
Federal Food, Drug, and Cosmetic Act (1938): 21 CFR 807.92(b)(1): **Biologics other than those regulated by CDER**	FDA
Federal Food, Drug, and Cosmetic Act (1938): **All routes of administration for small molecule drugs, protein therapeutics, and monoclonal antibodies**	FDA
Federal Food, Drug, and Cosmetic Act (1938): **Medical devices and radiation-emitting products**	FDA
Federal Food, Drug, and Cosmetic Act (1938): 21 C.F.R. §170, 21 C.F.R. §73, 21 C.F.R. §74, 21 C.F.R. §700, 21 C.F.R. §701, 21 C.F.R. §710, 21 C.F.R. §720, 21 C.F.R. §740: **Food ingredients and cosmetics**	FDA
Occupational Safety and Health Act (1970): 29 CFR 1910.1200: **Workplace materials and hazards**	OSHA

Agencies that Use Ocular and Dermal Data







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Eye Irritation: Private-Public Partnership

- Crop Life America-EPA-NICEATM
  - BASF, Dow, Bayer, Syngenta, Dupont
- Paired data for approximately 200 pesticides
- Rabbit eye test data + in vitro data in one or more assays:
  - Bovine corneal opacity and permeability (BCOP, OECD TG 437)
  - Isolated chicken eye (ICE, OECD TG 438)
  - EpiOcular (EO, OECD TG 492 and ET40 protocol)
  - Neutral red release (NRR)
  - Chorioallantoic membrane vascular assay (CAMVA)

Outcome

- A tiered approach using EO and NRR is promising, but not sufficient to identify all hazard categories
- BCOP did not appear to be useful for testing agrochemical formulations
- ICE and CAMVA datasets were too small for definitive assessments
- Overall, there is a need to conduct prospective *in vitro* testing
  - Protocol optimization
  - Data generation for specific formulation types

Skin Irritation: Private-Public Partnership

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

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Ongoing Ocular and Dermal Irritation Data Collection/Curation

- EPA FIFRA
- CropLife America (paired in vivo and in vitro ocular)
- Other stakeholders (EPA-led stakeholder discussions)
- Developing and evaluating QSAR models and where feasible to use in defined approaches

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Prospective Testing of Agrochemical Formulations

- Phase 1: small number (n=6) tested in all assays to demonstrate proof-of-concept
- Phase 2: comprehensive assessment of applicability with a larger set
  - Phase 2 study design and assays to be included contingent on Phase 1 results
- Coded formulations donated by companies
- Careful consideration of in vivo data
- Co-organized by NICEATM and PISC, with VMT members from ICCVAM and ODIWG, EURL ECVAM, PMRA, and industry

Eye Methods to be Evaluated

- BCOP
- ICE
- NRR
- EpiOcular (time to toxicity and TG 492 protocols)
- PorCORA (to evaluate reversibility of effects)

- Phase 1 testing ongoing

Additional Efforts

- Investigate the feasibility of developing new approaches, particularly for classes of substances that are poorly predicted by the existing models
  - Reflect on published work and OECD
  - Interrogate in vivo variability; build on Luechtefeld et al. 2016 and others
- Investigate incorporation of other data inputs
- Consider machine learning and other computational approaches, where feasible

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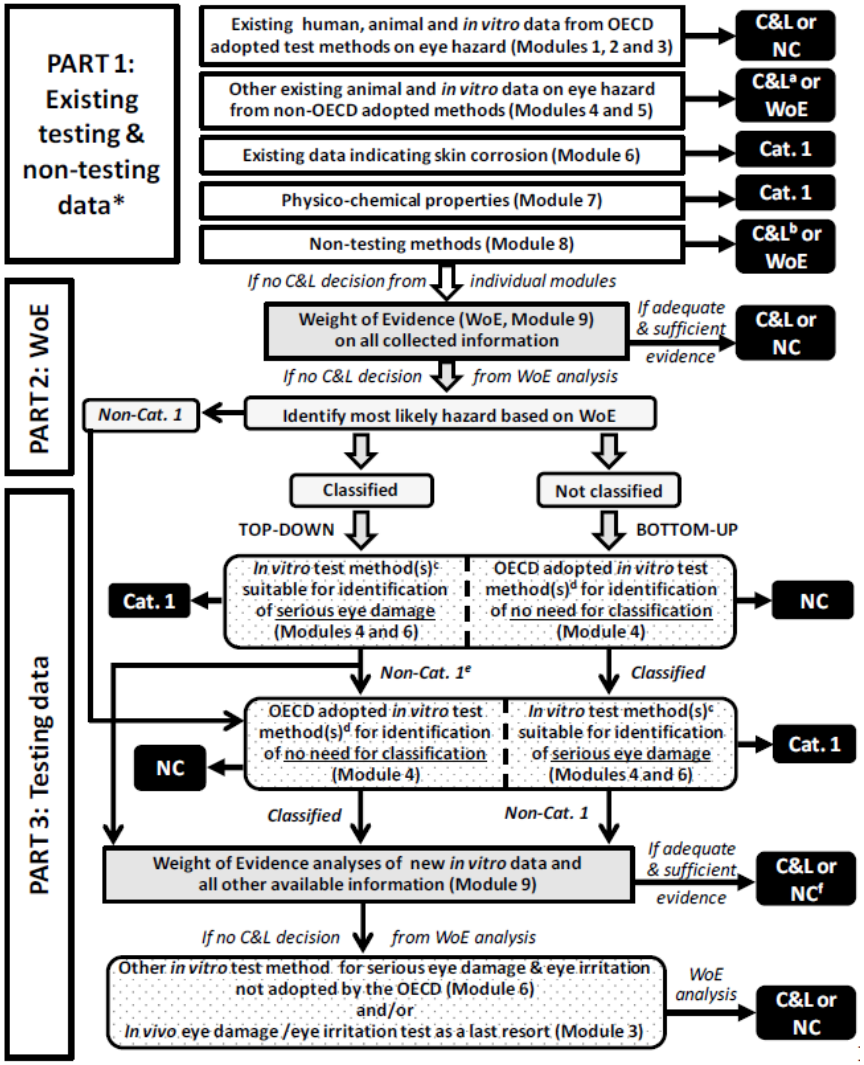
IATA for Eye Irritation: An International Effort

- OECD Guidance Document 263 (US and EU co-led project)
- Three parts:
  1. Existing and available information (physchem properties QSAR, read across, bridging)
  2. Weight of evidence
  3. New testing (in vitro and/or in vivo)



Scientific and Non-scientific Challenges

- Animal methods currently provide the reference data for evaluating alternatives
  - Results are variable
  - Need to identify summary metric & characterize uncertainty
- Data requirements vary across U.S. and global regulatory authorities and are often ambiguous
- Overcoming institutional inertia
  - Education and training, communication with method/model developers