



Interagency Coordinating Committee on the Validation of Alternative Methods

International Partner Updates

Anna Lowit, Ph.D.

EPA Office of Pesticide Programs

September 2, 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

International Partners - ICATM

- International Cooperation on Alternative Toxicological Methods



[National Institute of Environmental Health Sciences \(NIEHS\)](#)

For Immediate Release
Monday, April 27, 2009

Contact:
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Countries Unite to Reduce Animal Use in Product Toxicity Testing Worldwide *U.S., Canada, Japan and European Union Sign International Agreement*

Representatives from four international agencies, including the director of the U.S. National Toxicology Program (NTP), today signed a memorandum of cooperation that could reduce the number of animals required for consumer product safety testing worldwide. The agreement between the United States, Canada, Japan and the European Union will yield globally coordinated scientific recommendations on alternative toxicity testing methods that should speed their adoption in each of these countries, thus reducing the number of animals needed for product safety testing. The memorandum is available at http://iccvam.niehs.nih.gov/docs/about_does/ICATM-MOC.pdf.

“Signing this international agreement demonstrates our commitment to finding and advancing alternatives to animal testing,” said Linda Birnbaum, Ph.D., director of the NTP and National Institute of Environmental Health Sciences, part of the National Institutes of Health. “This agreement will help us achieve greater efficiency by avoiding duplication of effort and allowing us to leverage limited resources.”

Birnbaum signed as the U.S. representative on behalf of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), one of the national validation organizations participating in the agreement. Others who signed include Elke Anklam, Ph.D., for the European Centre for the Validation of Alternative Methods (ECVAM), David Blakey, D.Phil., for the Environmental Health Science and Research Bureau within Health Canada, and Masahiro Nishijima, Ph.D. for the Japanese Centre for the Validation of Alternative Methods (JaCVAM).

An ICATM Success: Workshop on Alternatives for Skin Sensitization

- First ever ICATM Workshop on the international regulatory applicability and acceptance of alternative non-animal approaches to skin sensitization assessment of chemicals used in a variety of sectors
- Agreed on actions to be undertaken by ICATM to promote the global use of non-animal approaches in the area of skin sensitization



Health Canada Update

- Health Canada is active in the area of New Approach Methodologies (NAMs) with the intentions to modernize approaches for prioritization and assessment and to advance efforts to implement the 3Rs of animal testing
- Working internationally to promote NAM development & application (e.g., with the OECD and the APCRA), and explore new approaches as case studies
 - Bisphenols – Development of a non-animal screening approach for endocrine disruption
 - Led revisions to the OECD TG 488 approved in April 2020 to update the recommended protocols for germ cell mutagenicity testing; revisions included a common sampling time for simultaneously assessing mutagenicity in somatic tissues and germ cells, thus significantly reducing the number of animals needed for testing
 - Development of an integrated, multi-assay (in vitro), higher throughput platform with accompanying bioinformatics integrated analysis tool for the assessment of chemically-induced genetic toxicity potential
 - Use of human liver spheroids and an “omics” approach for hazard identification and potency estimates for a group of PFAS
 - Development of the zebrafish embryo model as a whole organism NAM to transition from animal to non-animal models

Canadian Centre on Alternatives to Animal Methods CCAAM/CaCVAM

Officially opened the CCAAM laboratory (Eric S. Margolis Research & Training Laboratory for Alternatives to Animal Methods in October 2019) in October 2019 with a \$1 million donation from the Margolis family.



- Disease-in-a-Dish:
In vitro disease modelling with 3D-bioprinted tissue
- Diabetes-in-a-dish multi-tissue model



- Undergraduate/graduate course (Thinking outside the cage: non-animal methods in biomedical research and toxicology)
- Phasing out high school animal dissection

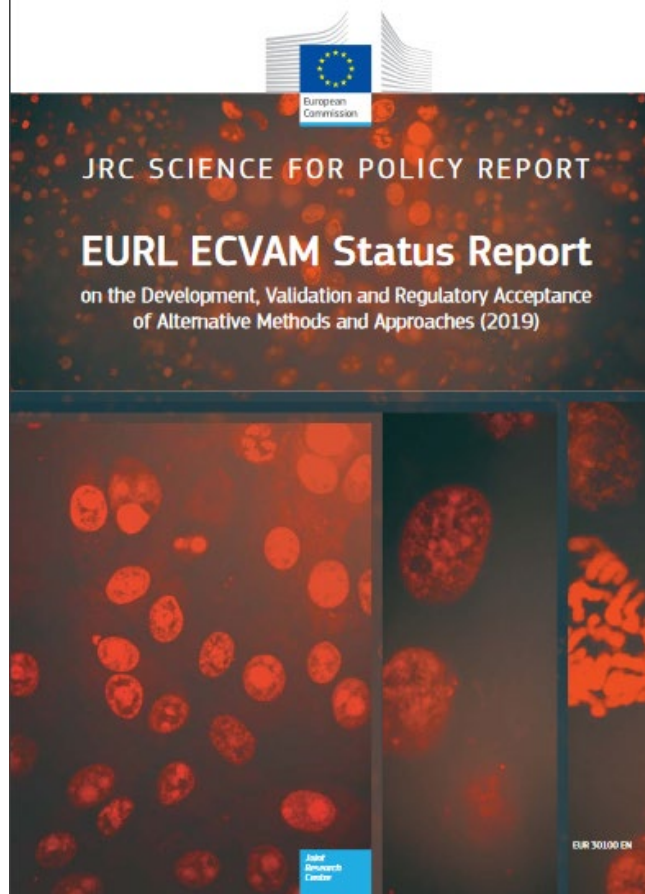


- Defined approach for animal-free contact lens safety testing
- Bridging toxicity testing from cells to populations: modelling acceptable human exposure levels from in vitro data

Some recent highlights from EURL ECVAM

- Publication of **EU report on the statistics on the use of animals for scientific purposes** (incl. data between 2015 and 2017)
- Publication of **EURL ECVAM Recommendation on non-animal-derived antibodies**
- Adoption of **OECD overview document on existing guidance for Integrated Approaches to Testing and Assessment** (led by EC through EURL ECVAM)
- Adoption of **updated OECD TG 458 on androgen receptor transactivation assays** (led by EC through EURL ECVAM)
- Publication of the **8th revision of the United Nations (UN) Globally Harmonised System of classification and labelling of chemicals (GHS)** incl. revised classification criteria for skin effects based on non-animal methods
- Publication of **21st revision of the UN Model Regulations** incl. non-animal testing in the criteria for classification of corrosives (proposal submitted by EURL ECVAM to the UN subcommittee on the Transport of Dangerous Goods)
- **ICATM workshop on “The Future of Alternative Methods for Regulatory Testing and their Contribution to Public Health”** (JRC, Ispra, Italy, 22 October 2019)

More highlights and information on our activities:



[10.2760/25602 \(online\)](https://ec.europa.eu/jrc/en/science-update/innovation-collaboration-education-drive-progress-alternatives-animal-testing)

<https://ec.europa.eu/jrc/en/science-update/innovation-collaboration-education-drive-progress-alternatives-animal-testing>

Highlights of the JaCVAM's activities



Main Progresses in 2019 to now

1. Immunotoxicity

MITA (Multi ImmunoToxicity Assay) consists of two assays

IL-2 Luc assay

- Validation study was completed (Jan. 2019).
- Peer review was just completed (Jun. 2020).
- Modified assay (IL-2 Luc leukocyte toxicity test) is in the prevalidation phase

IL-1 β Luc assay

- Validation report is being prepared.

2. Skin irritation

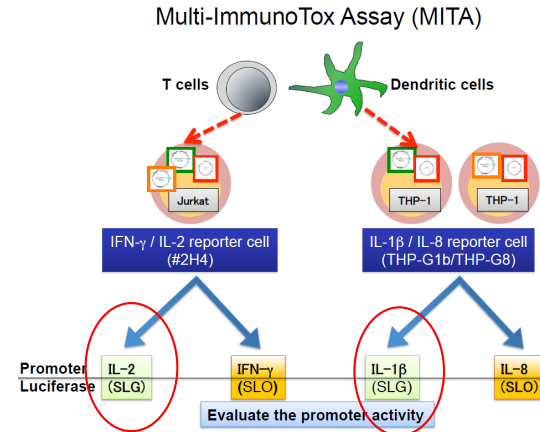
LbL 3D-Skin SIT

- Validation study was completed (Feb. 2020).
- Peer review report is being prepared.

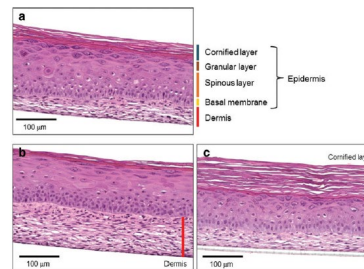
3. Skin sensitization

EpiSensA

- Experimental part is ongoing.



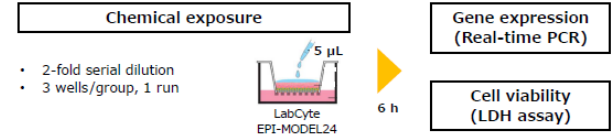
Layer-by-Layer (LbL) model: Dermo-epidermal human skin equivalents (DESEs) with dermis consisting of normal human dermal fibroblasts (NHDFs) and epidermis consisting of human keratinocytes



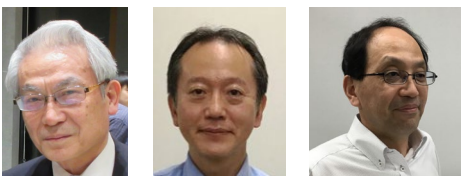
EpiSensA (Epidermal Sensitization Assay)

Saito et al., Toxicol. In Vitro 2017

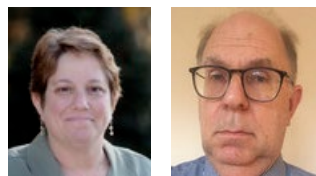
- **Vehicle** : Acetone:Olive oil = 4:1(AOO), Distilled water(DW), 50%EtOH
- selection criteria : a chemical is soluble at highest concentration
- selection priority : AOO \Rightarrow DW \Rightarrow 50%EtOH
- **Max. applied concentrations** . : Solid; 50(w/v)%, liquid; neat
- **Min. applied concentration** : 0.02%



Congratulations on the 20th anniversary of ICCVAM



ICATM

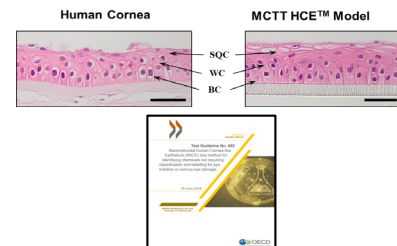


Joanna Matheson

Development of Alternative Test Methods

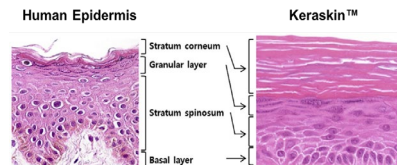
- **MCTT HCE™-Eye Irritation Test**

- MCTT HCE™ - EIT was developed for evaluating eye irritation potential with a reconstructed human cornea-like epithelium (RhCE), MCTT HCE™ model.
- Included in OECD TG 492 in 2019



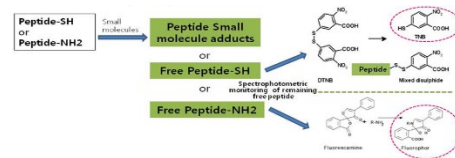
- **KeraSkin™-Skin Irritation Test**

- KeraSkin™-SIT is a *in vitro* test method for evaluating skin irritation using a new reconstructed human epidermis (RhE) model, KeraSkin™.
- Accepted onto the OECD work plan (04/2020) and international peer-review has been completed.



- **Spectrophotometric Direct Peptide Reactivity Assay-*In Chemico* Skin Sensitization Test**

- Spectrophotometric DPRA is a skin sensitization test method that improves the method of measurement of the existing *in chemico* DPRA(OECD 442C) by using spectrophotometer instead of HPLC. Its validation study is planned next year.



Current Adoption of Alternative Test Methods for Regulatory Use

- **3 OECD TGs were adopted for safety evaluation of cosmetics in 2019.**
 - **TG 442D** : *In Vitro* Skin Sensitisation: ARE-Nrf2 Luciferase Test Method
 - **TG 435** : *In vitro* Skin Corrosion: Membrane Barrier Test Method
 - **TG 431** : *In vitro* Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method



Act to Promote the Development, Dissemination, and Application of Alternative Methods

- **A draft act, applied to multiple government ministries, has been proposed to facilitate systematic and efficient development and implementation of alternative methods.**
 - The new legislation requires development of a comprehensive strategy to encourage development and utilization of alternative methods every 5 years, under which annual action plan will be established.
 - Also stipulates KoCVAM's role as a control tower and intergovernmental cooperation to help develop, spread and use alternative methods.



FIOCRUZ
Fundação Oswaldo Cruz

BraCVAM
Centro Brasileiro para Validação
de Métodos Alternativos
Brazilian Center for Validation of Alternative Methods

BraCVAM's major accomplishments over the last year

- Recommended the National Council of Control of Animal Experimentation (CONCEA) to make the Monocyte Activation Test (MAT) official in Brazil – published in September 2019
- Creation and Coordination of a *Latu sensu* post graduation program together with Instituto de Ciência e Tecnologia em Biomodelos/FIOCRUZ – first class started August 2019, ending in 2020. Second class will start March 2021


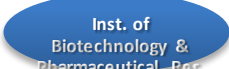


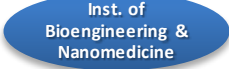


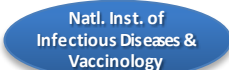




National Health Research Institutes, Taiwan

 <https://www.nhri.edu.tw/>



A **non-profit** research institute being supervised by **Ministry of Health and Welfare** and dedicated to explore the frontier of medical sciences for better health and welfare

8 Institutes and 2 Research Centers

Public Health and Policy Research	Biomedical Industrial Innovation Research	Basic and Translational Research
 Inst. of Population Health Sciences	 Inst. of Biotechnology & Pharmaceutical Res.	 Natl. Inst. of Cancer Research
 Natl. Inst. of Environmental Health Sciences	 Inst. of Bioengineering & Nanomedicine	 Inst. of Molecular & Genomic Medicine
 Special Units formed to meet the needs NHRI Forum	 Natl. Inst. of Infectious Diseases & Vaccinology	 Inst. of Cellular & System Medicine
 Mosquito-Borne Dis. Control Res. Center		 Immunology Research Center
		 Neuropsychiatric Research Center

150 Principal investigators, 1500 overall



Major Accomplishments of NHRI on Alternatives

Knowledge promotion

- International Symposium on Alternatives to Animal Testing 2019, Sept 17., Taipei, Taiwan (joined sponsor)
- Establishment of the Website of Taiwan Alternatives to Toxicity Testing



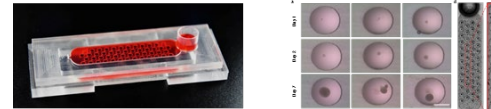
Research activity in NHRI

- ***In silico* modeling for developmental and reproductive toxicity**

Arch. Toxicol. 2020;94(2):485.

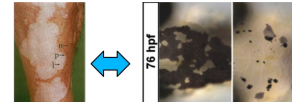
- **Cardiac spheroid organ-on-chip model**

Molecules 2016;21(7):882.



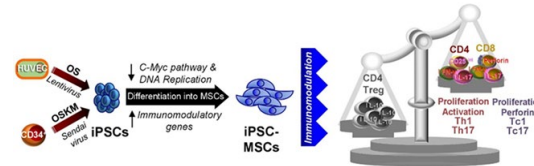
- **Zebrafish for depigmentation disease model**

J. Invest. Dermatol. 2020;140(2):404.



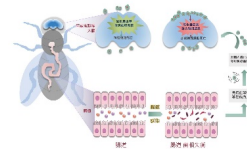
- **Human iPSC-MSCs platform**

Stem cells 2018;36(6):903.



- **A Drosophila model of gut-brain axis for study human neurological diseases**

Nature Commun. 2017;8: 24.





OECD 2020 PROGRESS

Bob Diderich
SACATM 2-3 September 2020



2020 progress on alternative methods for evaluating chemical safety

- Defined Approach for Skin Sensitisation (US/CA/EC)
 - International collaboration for curating and characterising human, mouse, in vitro and in silico data
 - Revised draft GL expected in 2020
- Defined Approach for Eye Irritation (FR)
 - Input on ~175 reference chemicals to benchmark predictive capacity of the DA
- In vitro assay battery for developmental neurotoxicity (US/EFSA)
 - Work to define regional regulatory needs
 - Work to define DNT +/- compounds for benchmarking and IVIVE
- Test Guideline using RT gill cell line to predict fish acute toxicity (NO/CH)
 - New proposed test guideline
 - Protocol and validation report to expert group for preliminary comments Q2 2020



2020 progress on policies and guidance for alternative methods

- Acceptance of computational data under MAD
 - Proposal to Joint Meeting for developing document
 - Includes MAD for data interpretation procedures (e.g., DAs) and for completely computational approaches (e.g., in silico models)
- Detailed review papers on:
 - Embryonic stem cells methods for developmental toxicity
 - In vitro approaches for developmental immunotoxicity
 - Retinoid signalling pathway focused primarily on mechanistic
 - Review of science and methods
 - May lead to proposals for DAs/in vitro battery

Comments from our International Partners?

