Non-Animal 6-Pack for Pesticide Testing: Update

Anna Lowit

Office of Pesticide Programs

US Environmental Protection Agency

March 11, 2019

Disclaimer: This presentation does not reflect the official position of any U.S. government agency

Acute Systemic Toxicity

ICCVAM Acute Toxicity Workgroup Roster

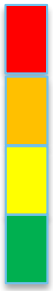
- Xinrong Chen (CPSC)
- John Gordon (CPSC)
- Joanna Matheson (CPSC)
- Lyle Burgoon (DoD)
- Donald Cronce (DoD, Co-chair)
- Natalia Garcia-Reyero (DoD)
- Jeffery Gearhart (DoD)
- David Mattie (DoD)
- Ronald Meris (DoD)
- Heather Pangburn (DoD)
- Brain Pate (DoD)
- Michael Phillips (DoD)
- Emily Reinke (DoD)
- Mark Williams (DoD)
- Aiguo Wu (DoD)
- Ryan Vierling (DOT)
- Tracy Keigwin (EPA, OPP)
- Anna Lowit (EPA, OPP)
- Edward Odenkirchen (EPA, OPP)
- Grace Patlewicz (EPA, ORD, Co-chair)
- Thao (Tina) Pham (EPA, OPP)
- Elissa Reaves (EPA, OPP)
- Jenny Tao (EPA, OPP)
- Tracy Chen (FDA, OCS)
- Warren Casey (NIEHS)
- Nicole Kleinstreuer (NIEHS)
- Elizabeth Maull (NIEHS)
- George Fonger (NLM)
- Pertti (Bert) Hakkinen (NLM)
- Surender Ahir (OSHA)
- Deana Holmes (OSHA)

ICATM Liaison Members
- Pilar Prieto Peraita (EURL ECVAM)
- Seung-Tae Chung (KoCVAM)

NICEATM Support Staff (ILS)
- Judy Strickland
- Agnes Karmaus
- David Allen

Agencies that Use Acute Oral Toxicity Data

Hazard



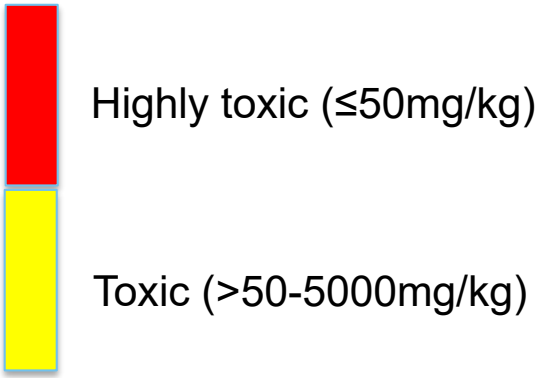
I (≤ 50mg/kg)

II (>50 ≤ 500mg/kg)

III (>500 ≤ 5000mg/kg)

IV (>5000mg/kg)

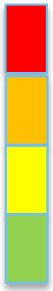
Hazard



Highly toxic (≤50mg/kg)

Toxic (>50-5000mg/kg)

Packing Group



I (≤ 5mg/kg)

II (>5 ≤ 50mg/kg)

III (>50 ≤ 300mg/kg)

IV (>300 ≤ 2000mg/kg)

Hazard

GHS

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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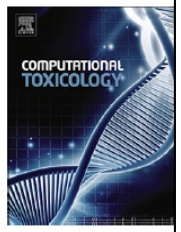
Predictive Models for Acute Oral Systemic Toxicity

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

Nicole C. Kleinstreuer[a], Agnes L. Karmaus[b], Kamel Mansouri[b], David G. Allen[b], Jeremy M. Fitzpatrick[c], Grace Patlewicz[c,*]

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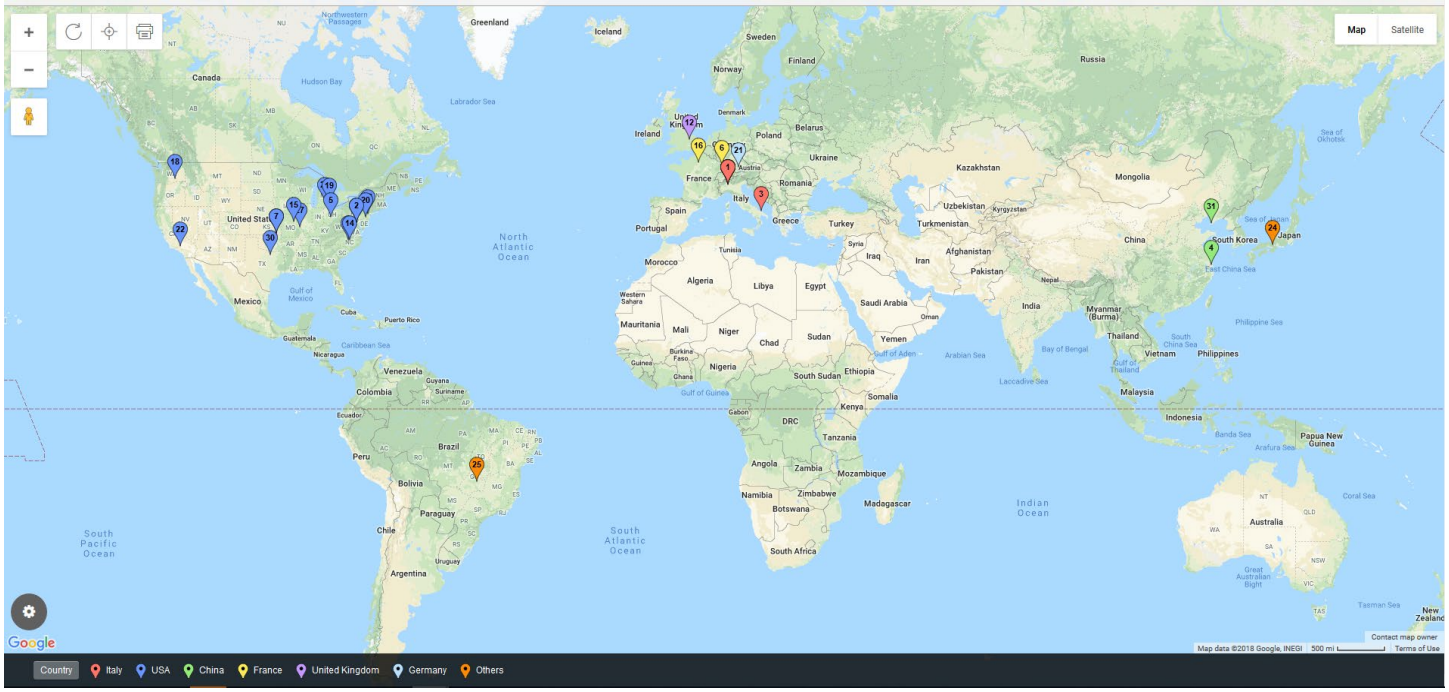
[c] National Center for Computational Toxicology (NCCT), Office of Research and Development, U.S. Environmental Protection Agency, 109 TW Alexander Dr, Research

- April 2018 workshop at NIH, USA
- https://ntp.niehs.nih.gov/go/tox-models

Consortium Comprised 35 Participating Groups

- Very Toxic: 32 models
- Non-toxic: 33 models
- EPA categories: 26 models
- GHS categories: 23 models
- LD50: 25 models

Total: 139 models



- Models were qualitatively and quantitatively assessed and combined into consensus models

Predictive Models for Acute Toxicity:

Performance vs Animal Data

Rat Oral LD50: Reproducibility | Consensus Model Performance (Tr/Ts Avg)

	Sensitivity	Specificity	BA	Sensitivity	Specificity	BA
VT	63%	99%	81%	77%	95%	86%
NT	96%	82%	89%	82%	92%	87%
EPA	74%	91%	82%	62%	94%	78%
GHS	66%	92%	79%	54%	92%	73%

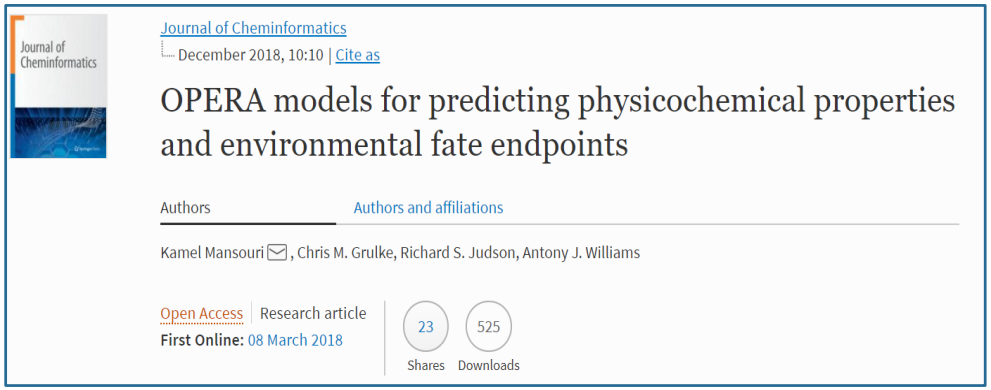
	R2	RMSE	R2	RMSE
LD50	0.8	0.42	0.74	0.42

Availability of Collaborative Acute Toxicity Modeling Suite (CATMoS)

- Consensus models for acute oral toxicity
- Implemented in OPERA v2.1; available on the NIEHS GitHub repository (https://github.com/NIEHS/OPERA/releases). Two versions:
  - Graphical user interface: *OPERA2.1_UI_win_web.zip*
  - Command line interface: *OPERA2.1_CL_win_web.zip*
- Predictions on US EPA's CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard) in the future
- Manuscript to be submitted for publication this Spring

OPERA
OPEn (q)saR App

Model	Property
AOH	Atmospheric Hydroxylation Rate
BCF	Bioconcentration Factor
BioHL	Biodegradation Half-life
RB	Ready Biodegradability
BP	Boiling Point
HL	Henry's Law Constant
KM	Fish Biotransformation Half-life
KOA	Octanol/Air Partition Coefficient
LogP	Octanol-water Partition Coefficient
MP	Melting Point
KOC	Soil Adsorption Coefficient
VP	Vapor Pressure
WS	Water solubility
RT	HPLC retention time



Recent Updates:

- Structural properties
- pKa
- Log D
- ER activity (CERAPP)

(https://ehp.niehs.nih.gov/15-10267/)

- AR activity (CoMPARA)

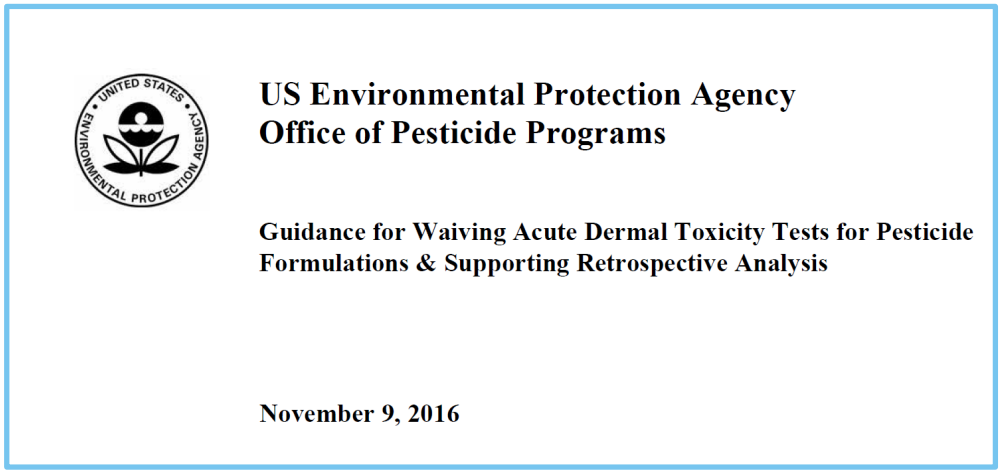
(https://doi.org/10.13140/RG.2.2.19612.80009, https://doi.org/10.13140/RG.2.2.21850.03520)

- Acute toxicity (CATMoS)

(https://doi.org/10.1016/j.comtox.2018.08.002)

Acute Dermal Pesticide Formulation Toxicity Testing

- Collaboration between EPA & NIEHS/NICEATM
- Analyze the relative contribution of data from acute oral and dermal toxicity tests to pesticide hazard classification and labelling
- Collected acute dermal and oral lethality data from rat studies with pesticide formulations
- EPA intends to expand the dermal waiver guidance to include technical ingredients (drafted and under review)


US Environmental Protection Agency
Office of Pesticide Programs

Guidance for Waiving Acute Dermal Toxicity Tests for Pesticide Formulations & Supporting Retrospective Analysis

November 9, 2016

Contents lists available at ScienceDirect

Toxicology in Vitro

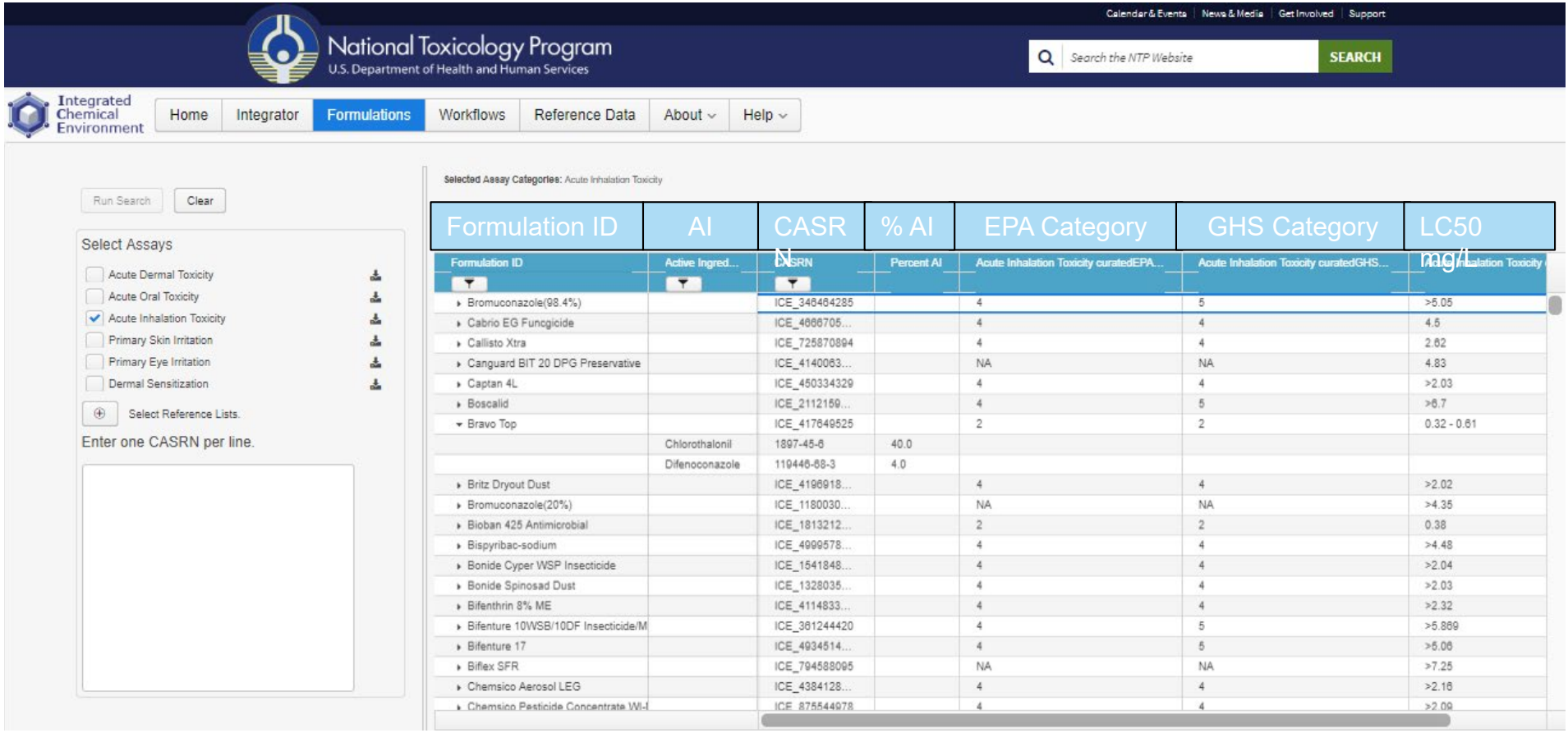
journal homepage: www.elsevier.com/locate/toxinvit

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

Amy J. Clippinger[a,*], David Allen[b], Annie M. Jarabek[c], Marco Corvaro[d], Marianna Gaça[e], Sean Gehen[f], Jon A. Hotchkiss[g], Grace Patlewicz[h], Jodie Melbourne[a], Paul Hinderliter[i], Miyoung Yoon[j], Dongeun Huh[k], Anna Lowit[l], Barbara Buckley[c], Daniel M. Wilson[g], Ian Indans[o], Mathieu Vinken[p]

- Workshop on Alternative Approaches for Acute Inhalation Toxicity Testing
- Co-organized by the PETA International Science Consortium and NICEATM

Establish a Database of Existing Acute Inhalation Toxicity Data



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

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]

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- John Gordon (CPSC)
- Eric Hooker (CPSC)
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- Timothy Varney (DOD)
- Evisabel Craig (EPA, OPP)
- Krystle Yozzo (EPA, OPP)
- Jenny Tao (EPA, OPP)
- Jill Merrill (FDA, CDER)
- Andrew J. McDougal (FDA, CDER)
- Donnie Lowther (FDA, CFSAN)
- Warren Casey (NIEHS)
- Nicole Kleinstreuer (NIEHS)
- Elizabeth Maull (NIEHS)

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- Deborah Ramsingh (Health Canada)

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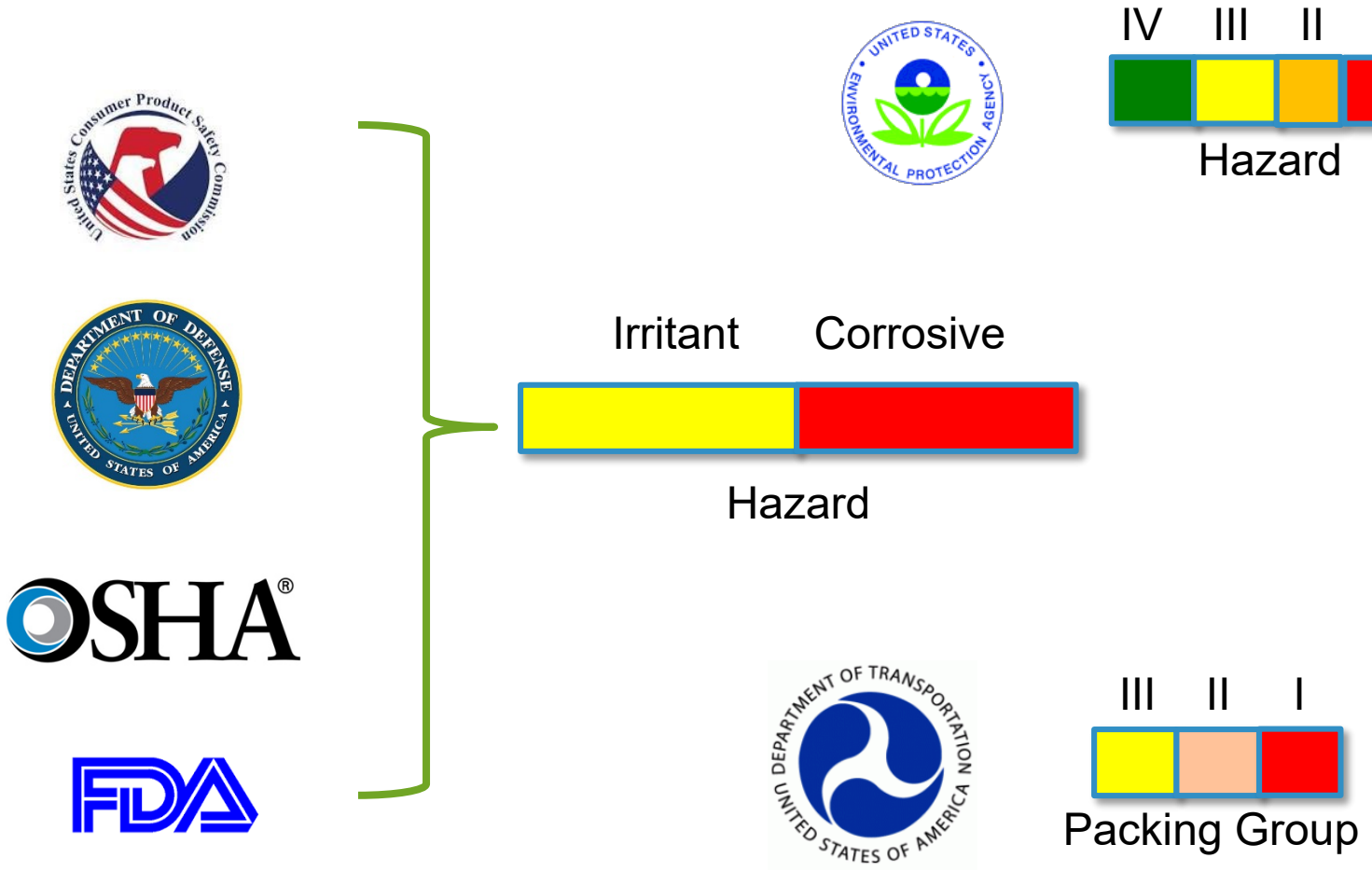
Agencies that Use Ocular and Dermal Data



CUTANEOUS AND OCULAR TOXICOLOGY
https://doi.org/10.1080/15569527.2018.1540494

Taylor & Francis
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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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Alternative Assays: Eye Irritation

- NICEATM analyzed paired *in vivo* and *in vitro* data for approximately 200 agrochemical formulations provided by 5 companies
- Conclusions:
  - Insufficient data from multiple assays to establish a defined approach
  - Prospective testing needed to fill data gaps

Prospective Testing

- Focus on the most common formulation types
  - suspension concentrates (SC)
  - emulsifiable concentrations (EC)
  - soluble liquids (SL)
- Balanced design with respect to hazard classification
- Careful consideration of available in vivo data
- Formulations donated by Crop Life America (CLA) partner companies
  - BASF; Bayer; FMC; Dow-DuPont (Corteva Agriscience); Monsanto; Syngenta
- Coded formulations distributed to testing labs by NTP

Methods Included in Prospective Testing

Test Method	OECD TG	Testing Laboratory
Bovine Corneal Opacity and Permeability	OECD TG 437	Institute for In Vitro Sciences
Neutral Red Release	-	Institute for In Vitro Sciences
Isolated Chicken Eye	OECD TG 438	Citoxlab
EpiOcular (EO) (EIT method)	OECD TG 492	MatTek
EO (Time-to-toxicity method; ET50-neat protocol)	-	MatTek
EO (Time-to-toxicity method; ET50-dilution protocol)	-	MatTek
Porcine Cornea Reversibility Assay	-	MB Research Labs

- Co-organized by NICEATM and the PETA International Science Consortium, with stakeholders from ICCVAM, ODIWG, EURL ECVAM, PMRA, and industry

Study Phases

Phase	Activities	Completion Dates

Pre-Study Phase	• Formation of stakeholder study group
	  ○ Scientists representing ICCVAM agencies, industry, and international regulatory and non-governmental organizations
	  ○ Assist with formulation procurement, study evaluation, and data review
	• Selection of *in vitro* test methods
		March 2018

Phase 1	• Testing of six formulations (three Category I/Category 1 and three Category IV/Not Classified formulations) in all *in vitro* test methods	September 2018
Phase 2	• Testing of 10 formulations in all *in vitro* test methods	March 2019
Phase 3	• Testing of approximately 30 formulations in selected *in vitro* test methods	September 2019

- **Funding to date provided by NICEATM, PISC, and CLA**

Study Status

- Phase 1 results showed that no single test method correctly classified all the pesticide formulations relative to classifications based on in vivo testing.
- Phase 2 testing is currently ongoing; pesticide formulations with a broader range of eye irritancy classifications than Phase 1 are being tested using all in vitro methods.
- Based on Phase 1 and 2 results, one or more of the test methods may be used in Phase 3 to test an expanded set of pesticide formulations.
  - The outcomes of this analysis will suggest endpoints that can form the basis of a defined approach for pesticide formulations testing for eye irritation/corrosion potential.

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

Additional Efforts

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

Skin Sensitization

ICCVAM Skin Sensitization Workgroup Roster

- Moiz Mumtaz (ATSDR)
- Patricia Ruiz (ATSDR)
- John Gordon (CPSC)
- Joanna Matheson (CPSC, Chair)
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- Evisabel Craig (EPA, OPP)
- David Lehmann (EPA, ORD)
- Anna Lowit (EPA, OPP)
- Timothy McMahon (EPA, OPP)
- Keith Salazar (EPA, OPPT)
- Louis (Gino) Scarano (EPA, OPPT)
- Simona Bancos (FDA, CDRH)
- Paul C. Brown (FDA, CDER)
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- Hon-Sum Ko (FDA, CDER)
- Diego Rua (FDA, CDRH)
- Stanislav Vukmanovic (FDA, CFSAN)
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- Nicole Kleinstreuer (NIEHS)
- Elijah Petersen (NIST)

ICATM Liaison Members
- Silvia Casati (EURL ECVAM)

NICEATM Support Staff (ILS)
- Jim Truax
- Judy Strickland
- David Allen

Skin Sensitization: U.S. Agency Requirements/Needs

	Accepted Animal Method	Evaluation Needs
Industrial chemicals	Not required	Hazard, risk
Pesticides	 LLNA	NS S Hazard
Workplace chemicals	 LLNA GPMT Buehler	NS 1B 1A Potency

Non-animal alternatives considered on a case-by-case basis

Skin Sensitization: U.S. Agency Requirements/Needs

		Accepted Animal Method	Evaluation Needs
FDA	Dermatologic products	 GPMT	Potency*
FDA	Medical devices	 GPMT	NS S Hazard
United States Consumer Product Safety Commission	Household products	  LLNA GPMT Buehler	NS S SS Potency

Non-animal alternatives considered on a case-by-case basis, except for medical devices.

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REGULATORY TOXICOLOGY

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

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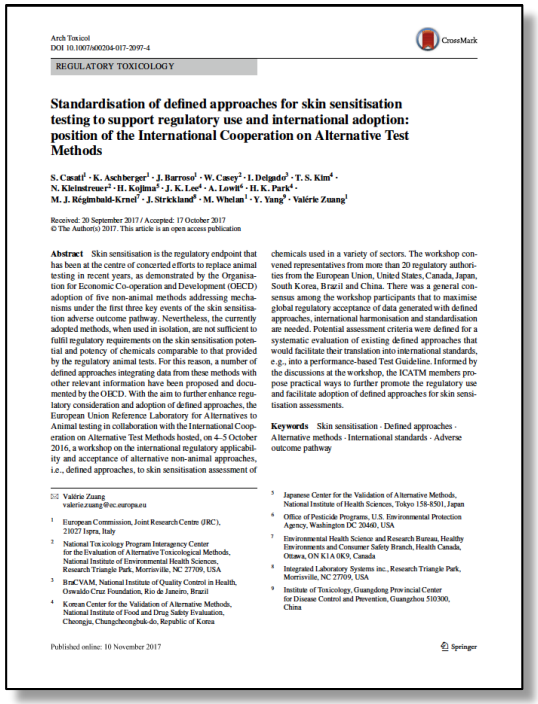
International regulatory requirements for skin sensitization testing

Amber B. Daniel[a], Judy Strickland[a,*], David Allen[a], Silvia Casati[b], Valérie Zuang[b], João Barroso[b], Maurice Whelan[b], M.J. Régimbald-Krnel[c], Hajime Kojima[d], Akiyoshi Nishikawa[d], Hye-Kyung Park[e], Jong Kwon Lee[e], Tae Sung Kim[e], Isabella Delgado[f], Ludmila Rios[g], Ying Yang[h], Gangli Wang[i], Nicole Kleinstreuer[j]

Global Skin Sensitization Project

- Objective: analysis of available non-animal defined approaches (DAs)
- NICEATM collaboration with Cosmetics Europe
  - Curation/generation of
    - in vivo LLNA and human data
    - in vitro cell-based data that maps to AOP
    - in silico computer predictions, chemical structural features & properties
- Qualitative and quantitative evaluation of OECD DAs as case studies (ICATM framework)
- Fully transparent approach (i.e., build open-source code packages)
- Evaluate performance against LLNA and human hazard/potency categories



Arch Toxicol
DOI 10.1007/s00204-017-2097-4

REGULATORY TOXICOLOGY

Standardisation of defined approaches for skin sensitisation testing to support regulatory use and international adoption: position of the International Cooperation on Alternative Test Methods

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Abstract Skin sensitisation is the regulatory endpoint that has been at the centre of concerted efforts to replace animal testing in recent years, as demonstrated by the Organisation for Economic Co-operation and Development (OECD) adoption of five non-animal methods addressing mechanisms under the first three key events of the skin sensitisation adverse outcome pathway. Nevertheless, the currently adopted methods, when used in isolation, are not sufficient to fulfil regulatory requirements on the skin sensitisation potential and potency of chemicals comparable to that provided by the regulatory animal tests. For this reason, a number of defined approaches integrating data from these methods with other relevant information have been proposed and documented by the OECD. With the aim to further enhance regulatory consideration and adoption of defined approaches, the European Union Reference Laboratory for Alternatives to Animal testing in collaboration with the International Cooperation on Alternative Test Methods hosted, on 4–5 October 2016, a workshop on the international regulatory applicability and acceptance of alternative non-animal approaches, i.e., defined approaches, to skin sensitisation assessment of chemicals used in a variety of sectors. The workshop convened representatives from more than 20 regulatory authorities from the European Union, United States, Canada, Japan, South Korea, Brazil and China. There was a general consensus among the workshop participants that to maximise global regulatory acceptance of data generated with defined approaches, international harmonisation and standardisation are needed. Potential assessment criteria were defined for a systematic evaluation of existing defined approaches that would facilitate their translation into international standards, e.g., into a performance-based Test Guideline. Informed by the discussions at the workshop, the ICATM members propose practical ways to further promote the regulatory use and facilitate adoption of defined approaches for skin sensitisation assessments.

Keywords Skin sensitisation · Defined approaches · Alternative methods · International standards · Adverse outcome pathway

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[6] Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington DC 20460, USA
[7] Environmental Health Science and Research Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, ON K1A 0K9, Canada
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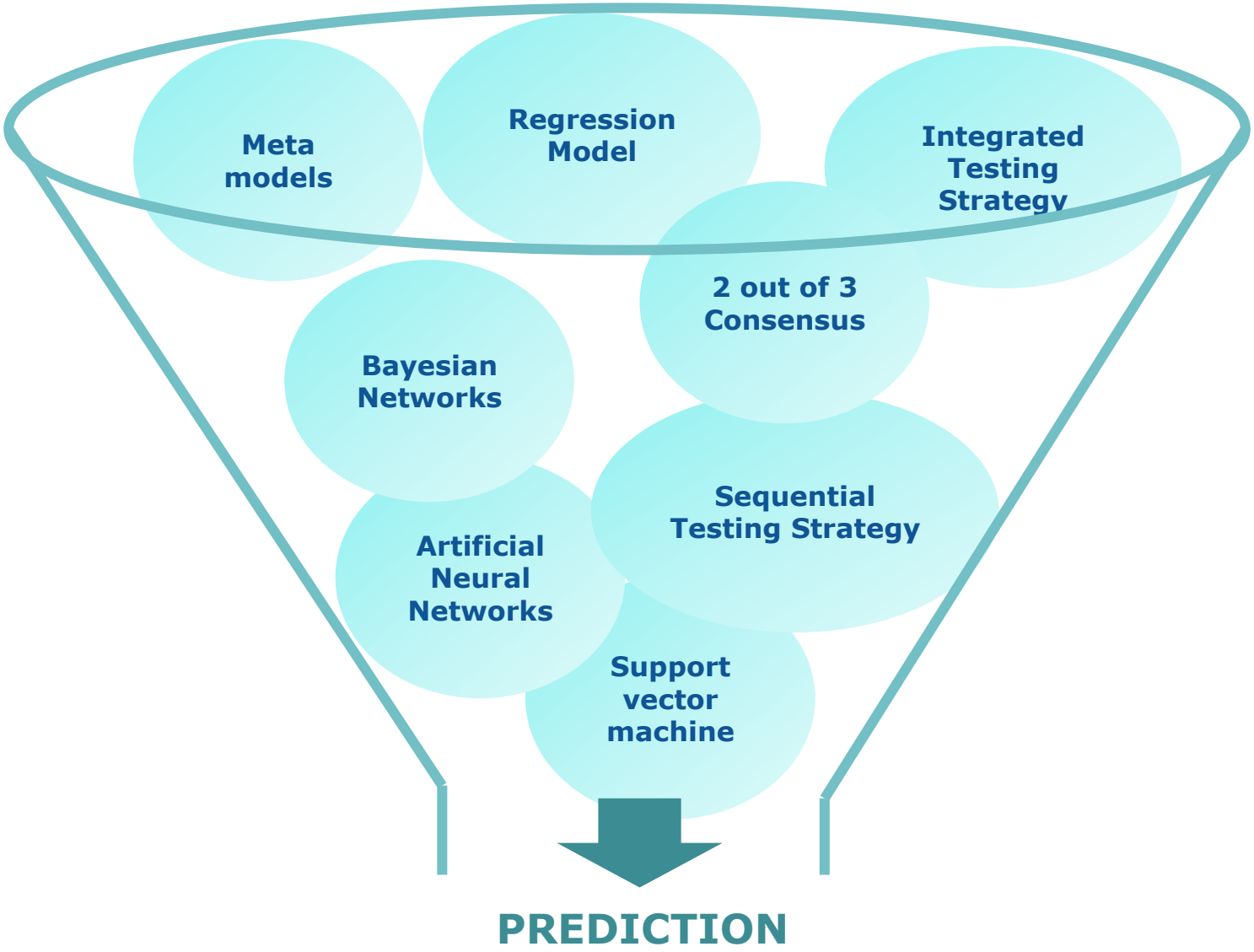
Springer

Hoffmann et al. 2018 Crit Rev Tox
Kleinstreuer et al. 2018 Crit Rev Tox

Types of Defined Approaches



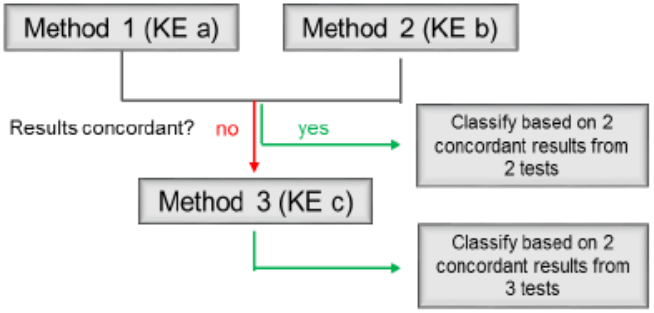
Draft Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing

- Announced April 10, 2018 & describes the science that supports a policy to accept alternative (in vitro, in silico, in chemico) approaches for identifying skin sensitization hazard in place of animal studies.
  - Multiple non-animal testing strategies - *in vitro, in chemico*, and *in silico* inputs demonstrate comparable or superior performance to the laboratory animal studies.
  - Public comment period ended on June 9, 2018.
- The interim policy is the result of collaboration between
  - Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
  - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
  - European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)
  - Health Canada (PMRA)

Draft Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing

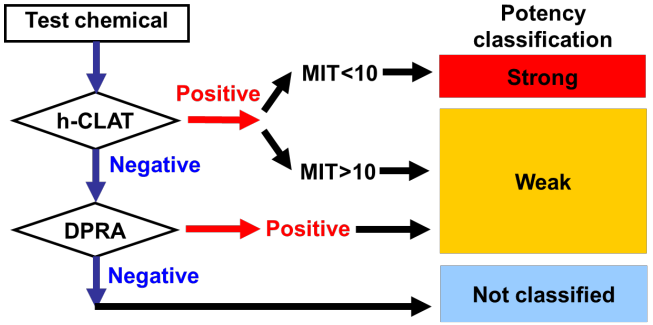
2 out of 3

- No differential weighting of individual test methods, or defined sequential order of testing



Sequential Testing Strategy

- Prediction can be derived after first tier
- Depends on KE3 (e.g. hCLAT) and KE1 (e.g. DPRA)



International Harmonization

- OECD proposal (SPSF) co-led by US, EU, and Canada
  - Create a performance based test guideline for non-animal defined approaches to skin sensitization testing
  - Included in OECD workplan April 2017, update provided April 2018
- Special sessions of the OECD national coordinators in Dec 2017 & 2018 to review progress and discuss next steps
  - Achieved consensus on evaluation framework for DA assessment
  - Formed expert group on skin sensitization DAs, including subgroups on uncertainty and applicability domain
  - Expert review of simple, rule-based DAs complete (June 2018)
  - DA GL drafted (September 2018)
  - Progress update WNT April 2019

OECD BETTER POLICIES FOR BETTER LIVES

Expanding Coverage of Chemical Space

- NTP is supporting testing other types of chemicals in three alternative test methods: DPRA, KeratinoSens™, h-CLAT
- NTP has procured approximately 235 chemicals including: pesticides, agrochemical formulations, dermal excipients, personal care product ingredients, “challenge” chemicals
- Chemical nominations from multiple agencies
  - EPA Office of Pesticides, Office of Pollution Prevention and Toxics, and Office of Research and Development
  - Consumer Product Safety Commission
  - Food and Drug Administration
  - NTP

EPA's Office of Pesticide Programs (OPP) is hiring
Stop by the EPA ORD Booth (#4065)
OPP representatives will be there:
Monday 1:30-2:30
Tuesday 2:30-3:30
Wednesday 10:30-12:00

USAjobs announcement#:
09/11 is R-OCSPP-DE-2019-0036
12/13 is R-OCSPP-DE-2019-0037