Update from EPA's Office of Pesticide Programs

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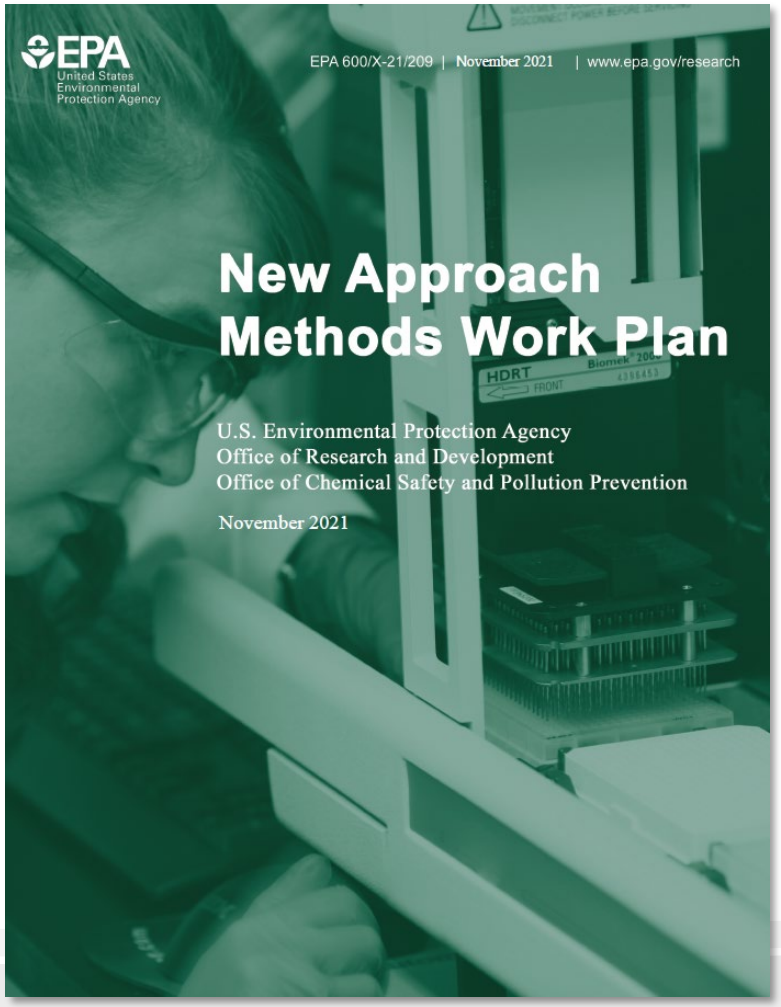
Disclaimer: The views expressed in this presentation are those of the author(s) and do not necessarily represent the views or policies of the Agency.

EPA NAM Work Plan



- Five objectives for achieving the reduction goals while ensuring that Agency decisions remain fully protective of human health and the environment
  - Evaluate regulatory flexibility
  - Develop baselines and metrics
  - **Establish scientific confidence** and demonstrate application
  - Develop NAMs to address information gaps
  - Engage and communicate with stakeholders
- Changes in 2021 updated work plan:
  - Modified timelines & deliverables through 2024; two case studies
  - Covered species now includes all vertebrate animals, consistent with TSCA
  - Pilot study to develop NAMs training courses for a broad range of stakeholders

Regulatory Toxicology and Pharmacology
Volume 71, Issue 3, April 2015, Pages 463-477

Proposing a scientific confidence framework to help support the application of adverse outcome pathways for regulatory purposes

Grace Patlewicz [a]
Richard A. Becker [d]

Unclassified

ENV/JM/MONO(2007

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

30-Mar-200

English, Fren

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

Arch Toxicol (2018) 92:611–617
https://doi.org/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

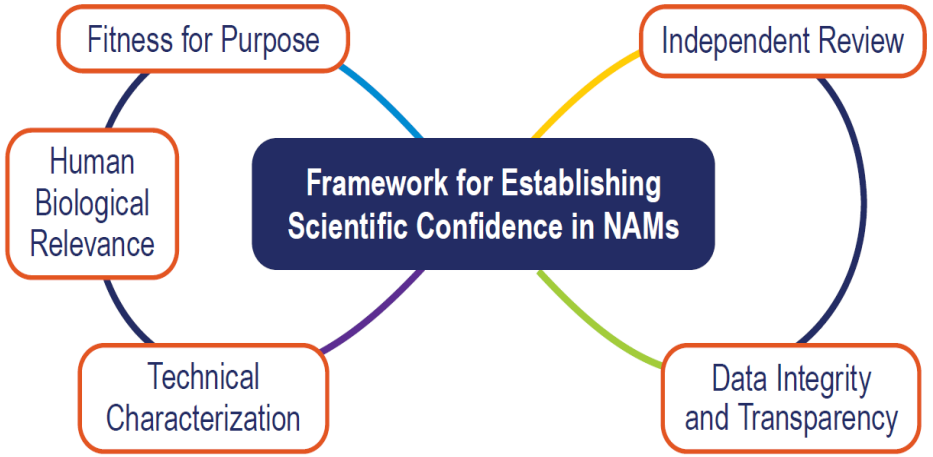
S. Casati[1] · K. Aschberger[1] · J. Barroso[1] · W. Casey[2] · I. Delgado[3] · T. S. Kim[4] · N. Kleinstreuer[2] · H. Kojima[5] · J. K. Lee[4] · A. Lowit[6] · H. K. Park[4] ·

Archives of Toxicology
https://doi.org/10.1007/s00204-022-03365-4

REVIEW ARTICLE

A framework for establishing scientific confidence in new approach methodologies

Anna J. van der Zalm[1] · João Barroso[2] · Patience Browne[3] · Warren Casey[4] · John Gordon[5] · Tala R. Henry
Nicole C. Kleinstreuer[7] · Anna B. Lowit[6] · Monique Perron[8] · Amy J. Clippinger[1]



Extracted from van der Zalm, A.J., et al. 2022

OECD Series on Testing and Assessment

Guidance Document on Good In Vitro Method Practices (GIVIMP)

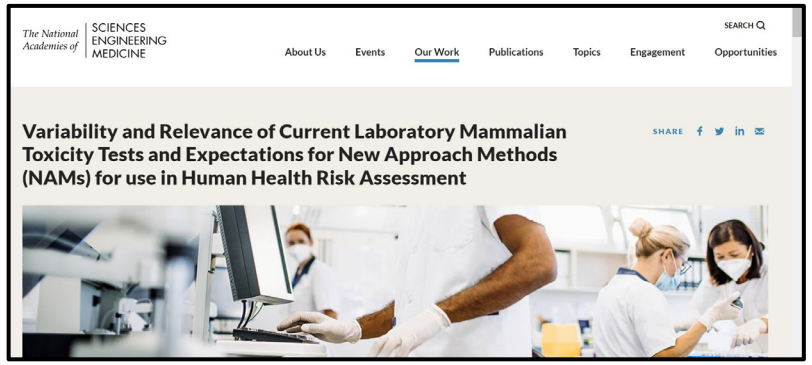
Essential Elements of Framework

<u>Goal of scientific confidence framework:</u>

To develop a more generalizable scientific confidence framework that is applicable across a broad range of NAMs and Agency decision contexts

Graphic developed by Dr. A. Harrill (ORD) and inspired by figure in van der Zalm *et al.* 2022.

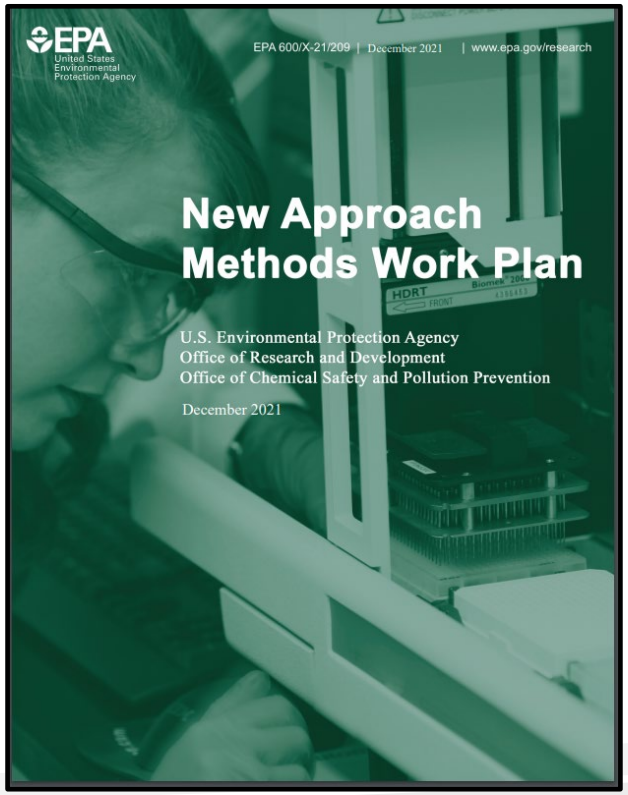
On-Going Activities Related to the Development of Confidence Building & Validation Frameworks



NAS review of validation and scientific confidence frameworks for NAMs

UNITED STATES ICCVAM Advancing Alternatives to Animal Testing

ICCVAM Validation Workgroup



2021 US EPA NAMs Workplan: Establish Scientific Confidence in NAMs

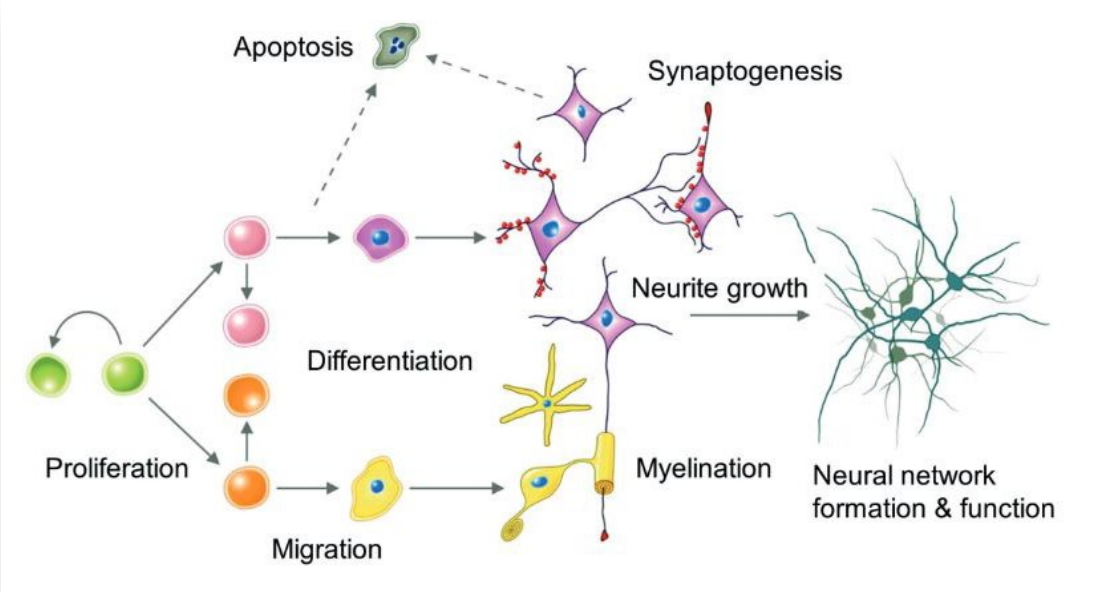
https://www.epa.gov/chemical-research/epa-new-approach-methods-work-plan-reducing-use-vertebrate-animals-chemical

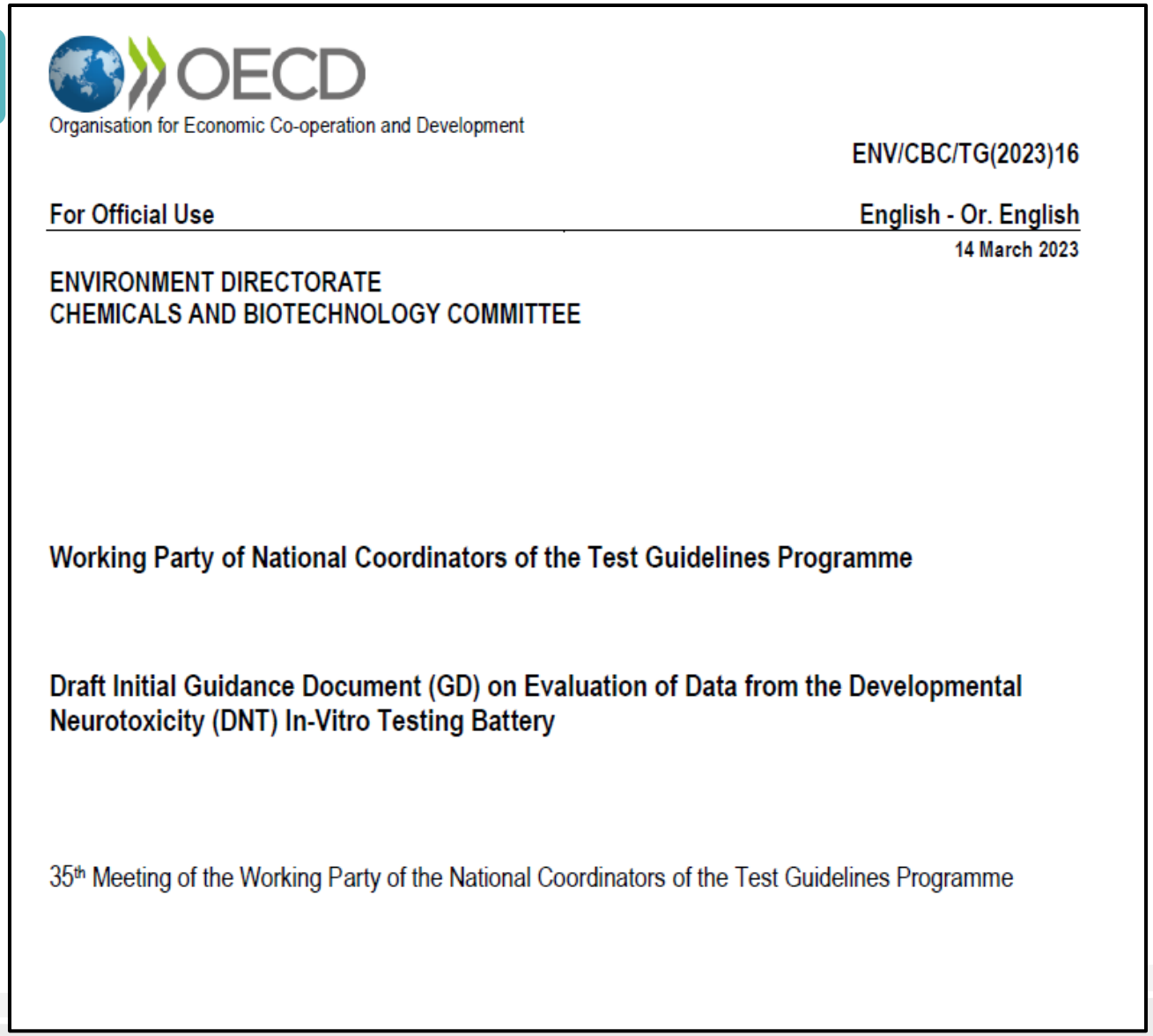
2022 Conference on the State of the Science on Development and Use of New Approach Methods (NAMs) for Chemical Safety Testing October 12-13, 2022

https://www.epa.gov/chemical-research/epa-nams-conference

Developmental Neurotoxicity (DNT)

- International effort to develop DNT NAM battery to assess critical processes of neurodevelopment
- Convened FIFRA SAP in 2020: https://www.epa.gov/sap/use-new-approach-methodologies-nams-derive-extrapolation-factors-and-evaluate-developmental
    - Response to SAP released in March 2023: https://www.regulations.gov/document/EPA-HQ-OPP-2020-0263-0057





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ENV/CBC/TG(2023)16

For Official Use — English - Or. English

14 March 2023

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CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Working Party of National Coordinators of the Test Guidelines Programme

Draft Initial Guidance Document (GD) on Evaluation of Data from the Developmental Neurotoxicity (DNT) In-Vitro Testing Battery

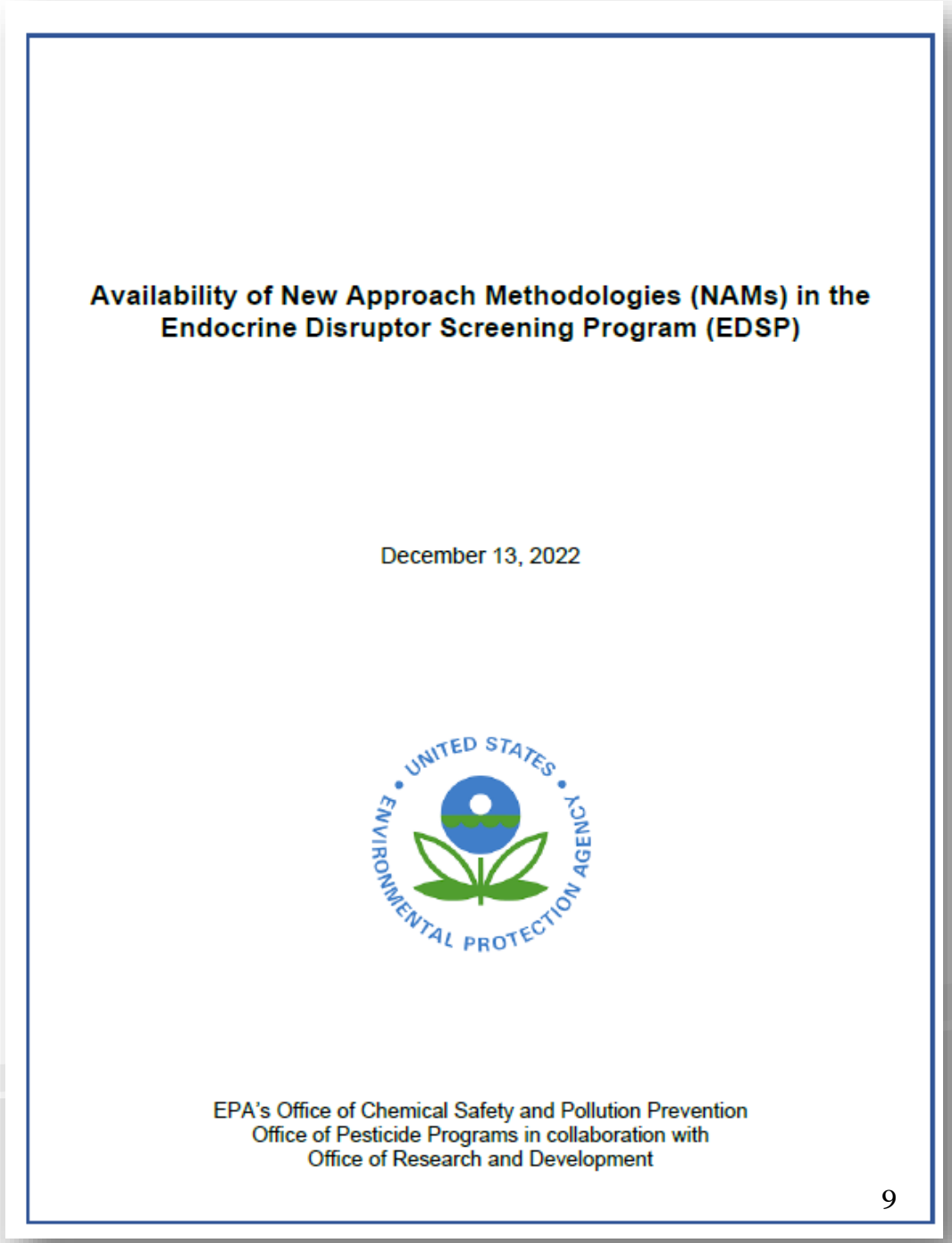
35th Meeting of the Working Party of the National Coordinators of the Test Guidelines Programme

EPA

- OECD guidance document on evaluation of DNT battery data adopted in April 2023
- Continued testing coordinated by NTP
  - Chemical nominations from OPP
- Data from *in vitro* DNT testing used in weight-of-evidence analysis to support need for additional DNT data
  - https://www.regulations.gov/document/EPA-HQ-OPP-2016-0141-0033

NAMs for EDSP

- Whitepaper recently released on available NAMs to inform endocrine disruptor screening program (EDSP)
  - Released Jan 2023 with 60 day public comment period
- ER (18 assay battery) and AR (11 assay battery) pathway models as alternatives for particular Tier 1 screening assays
- Additional models and assays for priority setting or for consideration as other scientifically relevant information (OSRI) for weight of evidence evaluations
- Ongoing research with Office of Research and Development (ORD)



Availability of New Approach Methodologies (NAMs) in the Endocrine Disruptor Screening Program (EDSP)

December 13, 2022

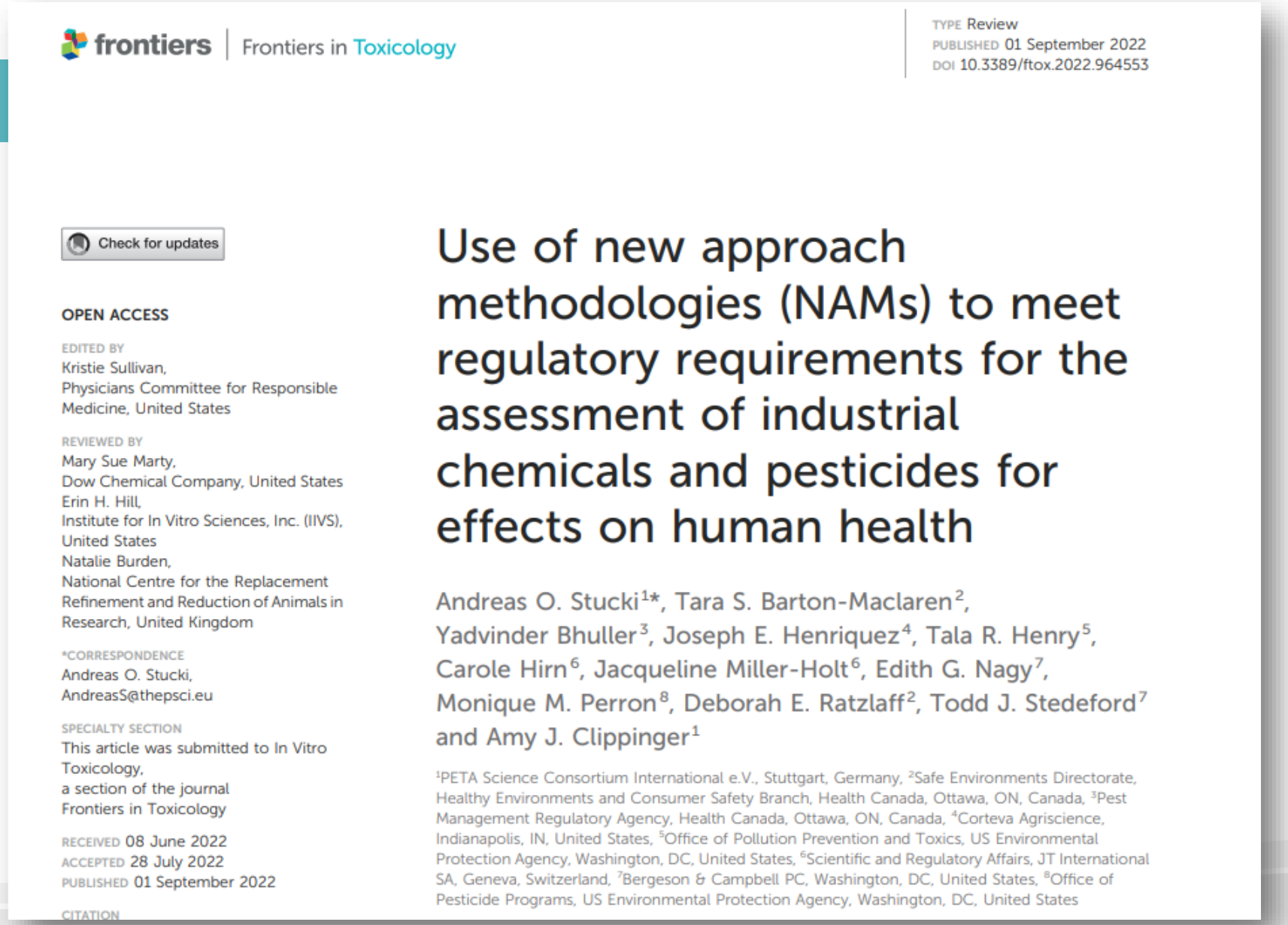
EPA's Office of Chemical Safety and Pollution Prevention
Office of Pesticide Programs in collaboration with
Office of Research and Development

Reducing Use of Dog Studies

- 2021 Center for Alternatives to Animals Testing (CAAT) hosted workshop on the challenges and opportunities for overcoming dog use in agrochemical evaluation and registration
  - Bishop et al. (2023) DOI: 10.14573/altex.2302151
- Coordinating efforts through Health and Environmental Sciences Institute (HESI) workgroup
- OPP currently working on retrospective analyses
  - Requesting similar analyses from other organizations
- Continued engagement with registrants on potential use of kinetic and/or *in vitro* data

Defined Approaches for Eye Irritation

- Previous work on eye irritation
  - Policy to accept eye irritation assays for antimicrobial cleaning products: https://www.epa.gov/pesticide-registration/alternate-testing-framework-classification-eye-irritation-potential-epa
  - Prospective and Retrospective Evaluation of the Eye Irritation Potential of Agrochemical Formulations (NIH 2021)
  - Manuscript published evaluating human relevance, strengths, and uncertainties of *in vivo* and *in vitro* studies (Clippinger et al. 2021)
    - Many *in vitro*/*ex vivo* methods are equivalent or scientifically superior to *in vivo* rabbit study
- Defined approaches for eye irritation for agrochemical formulations
  - Collaboration with NICEATM, PETA, and IIVS
  - Manuscript in preparation



frontiers | Frontiers in Toxicology

TYPE Review
PUBLISHED 01 September 2022
DOI 10.3389/ftox.2022.964553

Check for updates

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to In Vitro Toxicology,
a section of the journal
Frontiers in Toxicology

RECEIVED 08 June 2022
ACCEPTED 28 July 2022
PUBLISHED 01 September 2022

CITATION

Use of new approach methodologies (NAMs) to meet regulatory requirements for the assessment of industrial chemicals and pesticides for effects on human health

Andreas O. Stucki[1]*, Tara S. Barton-Maclaren[2], Yadvinder Bhuller[3], Joseph E. Henriquez[4], Tala R. Henry[5], Carole Hirn[6], Jacqueline Miller-Holt[6], Edith G. Nagy[7], Monique M. Perron[8], Deborah E. Ratzlaff[2], Todd J. Stedeford[7] and Amy J. Clippinger[1]

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Review article by Stucki et al. (2022)

https://doi.org/10.3389/ftox.2022.964553

Ecotoxicity Retrospective Analyses

- Fish acute retrospective
  - OPP uses cold freshwater fish, warm freshwater fish, and saltwater fish to assess acute risks (200 fish or more used)
  - Is there a consistently more sensitive fish across all compounds and can we reduce data sets to two or even one fish study?
  - Manuscript recently published: https://doi.org/10.1016/j.yrtph.2023.105340
- Avian reproductive retrospective
  - Currently 2 species are required: Mallard Duck and Bobwhite Quail
  - Could a protective risk assessment be done with only one species?
  - Currently in data curation and exploration stage

Ecotoxicity Modeling

- Collaborative Acute Toxicity Modeling Suite (CATMoS)
  - 35 participants/groups from around the globe representing academia, industry, and government contributed to the development
  - Evaluate potential replacement of rat acute oral toxicity study with LD_{50} predictions
    - Promising results for identifying non-toxic chemicals (LD_{50} > 2000 mg/kg)
  - Manuscript in preparation

Strategic Vision for Adopting New Approach Methodologies

Overview

To better protect human health and the environment, EPA's Office of Pesticide Programs (OPP) is developing and evaluating new approach methodologies (NAMs) in molecular, cellular and computational sciences to supplement or replace more traditional methods of testing chemicals — such as animal testing — for potential hazards. OPP is enhancing its ability to use these new methods such as integrated approaches to testing and assessment (IATA). IATA promotes a hypothesis-based, systematic, integrative use of exposure and hazard information.

Adopting 21st Century Methodologies for risk assessment and toxicology review purposes is built upon the "three Rs": reduction, replacement and refinement.

Quick Resources

- Metrics
- Strategies to Reduce Animal Testing
- Strategies to Replace Animal Testing

https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-new-approach-methodologies

Thank You