

# Overview of USEPA OPP's Activities to Reduce Animal Use and Implement Alternative Approaches – ICCVAM Public Forum

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# Guiding Principles for Data Needs for Pesticides

- Guiding Principles for Data Requirements
  - Purpose: provide consistency in the identification of data needs, promote and optimize full use of existing knowledge, and focus on the critical data needed for risk assessment.
  - <https://www.epa.gov/pesticide-registration/guiding-principles-data-requirements>
- “...ensure there is sufficient information to reliably support registration decisions that are protective of public health and the environment while avoiding the generation and evaluation of data that does not materially influence the scientific certainty of a regulatory decision....”
- “...avoid unnecessary use of time and resources, data generation costs, and animal testing.”



# Guiding Principles for Data Needs for Pesticides

- Flexibility in implementing Part 158 data requirements (§158.30):
  - **Waivers may be granted** as permitted by 40 CFR Part 158.45;
  - Additional data beyond the 158 data requirements may be important to the risk management decision (§158.75), **alternative approaches can be accepted**, and other data can be used.



# Modernizing Acute Toxicity “6 Pack”

- Letter to Stakeholders on OPP’s Goal to Reduce Animal Testing from Jack E. Housenger, Director.
  - <https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2016-0093-0003>
  - Working in partnership with other governmental entities, industry and non-governmental organizations (NGOs) and need continued robust participation and support to achieve our mutual goal.
  - Activities fall under three main objectives
    - Critically evaluating which studies form the basis of OPP decisions;
    - Expanding acceptance of alternative methods and;
    - Reducing barriers such as challenges of data sharing among companies and international harmonization to adopting alternative methods in the U.S. and internationally.



# Modernizing the Acute Toxicity “6 Pack”

- Stakeholder group is meeting regularly to discuss progress, goals, & opportunities to work together
- If you are interested in joining the stakeholder group:
  - Contact Shannon Jewell (703-347-0109, [jewell.shannon@epa.gov](mailto:jewell.shannon@epa.gov))
- Integrated Approaches to Testing and Assessment (IATA) docket:
  - [EPA-HQ-OPP-2016-0093](#)
  - The docket includes stakeholder meeting notes, presentations, and several policy documents from the past few years.



# Alternative Assays: Eye Irritation

- Currently have a policy in place to accept eye irritation assays for antimicrobial cleaning products
- Effort to extend the use of alternative assays for other classes of pesticides
- Voluntary data collection effort for conventional pesticides
  - >200 pairs of in vitro-in vivo data provided by industry
- Prospective testing to fill in the gaps:
  - Phase 1 evaluated 6 formulations donated by industry (along with reference in vivo data) in BCOP, EpiOcular, NRR, PorCORA, ICE assays
  - Phase 2 testing of 10 formulations donated by industry in BCOP, EpiOcular, NRR, PorCORA, ICE is ongoing
  - Phase 3 will then test additional formulations donated by industry
  - Co-chaired by PETA-ISC and NICEATM, with members from PCRM, EPA, PMRA, ECVAM, and Industry



## International Cooperation on Alternative Test Methods (ICATM) – Skin Sensitization

- OECD proposal (SPSF) co-led by US, EU, and Canada submitted November 2016
  - Create a performance based test guideline for non-animal defined approaches to skin sensitization testing
  - Included in OECD workplan April 2017
- Special session of the OECD national coordinators (WNT) met in December 2017 to review progress and discuss next steps
  - Achieved consensus on evaluation framework
  - Formed expert group on skin sensitization
- Expert group has been meeting regularly



# International Cooperation on Alternative Test Methods (ICATM) – Skin Sensitization (cont'd)

- The Science supports moving forward:
  - Multiple non-animal testing strategies - *in vitro*, *in chemico*, and *in silico* inputs demonstrate *comparable or superior performance* to the mouse LLNA.
  - An assessment framework for integrated non-animal approaches that could *serve as replacements* for the current animal test.





## *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.
- 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*

- EPA is accepting these approaches immediately under certain conditions described in the interim policy.
  - Existing OECD guidelines for determining hazard (only)
  - Approaches for combining results of 2 or 3 assays described in the draft, interim policy
  - Active or inert ingredients (not formulations yet)
- On-going work at NTP to evaluate use of OECD guidelines on formulations/mixtures
  - Will revise policy in the future as appropriate
- Comments on the draft skin sensitization policy were solicited this summer however the comments are still being evaluated



# Dermal Absorption Triple Pack

- Triple packs
  - Human *in vitro*, rat *in vitro*, and rat *in vivo* studies using similar protocols (e.g., same test material, doses)
  - Used by OPP to refine dermal assessments by adjusting for differences between *in vitro* and *in vivo* absorption as well as species differences
- NICEATM/ILS is in the process of compiling data from triple pack studies
  - Assessing possibility of using human *in vitro* study only for risk assessment
- Industry partners are also providing triple pack data for inclusion (three assays received to date)
- Team plans to summarize any trends seen in the data within and across the three assays and determine how (if at all) a risk assessment would change if the evaluation was based solely on *in vitro* data



# Carcinogenicity: Development of Guidance and Waiver Criteria

- OPP is currently collaborating with industry and non-government organizations
- Workgroup is considering:
  - Different chemistries
  - Modes of action
  - Use patterns/exposures
  - Metabolic profiles
- Goal: Develop waiver criteria for rodent carcinogenicity studies



# Important considerations in the development of guidance and waiver criteria for cancer evaluation

- What is known about the class of chemistry?
- Metabolic profile/ADME and TK
- Mutagenic concern?
- Short-term toxicity data
  - Toxicity observed, target cells/organs, endocrine activity, etc.
- Mode of action information (pesticidal and tumor MOAs)
- Data informing human relevance
- Read across information/Structure Activity Relationships (SAR)
- Margins of exposure based on use pattern/exposure information



## Avian subacute/acute risk retrospective

- OPP ecological risk assessments use both acute oral and sub-acute dietary studies to assess acute risks to birds (the endpoint that results in the highest risk quotient drives the risk conclusion)
- Question: Can we confidently assess acute risk for birds using a reduced suite of effects studies focusing on the single oral dose protocol?
  - How often have subacute dietary risk quotients (RQs) quantitatively driven risk assessment conclusions?
- Partnership with PETA



# Avian subacute/acute risk retrospective cont'd

- Looked at chemicals that came into the Registration Division (RD) for registration from 1998-2016
- Bottom line results are that 99% (118 of 119) of all subacute dietary studies for new use assessments did not change risk conclusions already reached using oral dose-based RQ's.
  - In most cases (there are some exceptions) a robust avian acute risk assessment can be conducted without the sub-acute dietary studies.
- Peer-reviewed scientific journal publication (PETA lead, Agency coauthors)
  - <https://doi.org/10.1016/j.yrtph.2019.03.013>
- Next Step:
  - Draft policy instructions is currently being developed for risk assessors and risk managers and will be released for public comment



## Fish acute retrospective

- OPP ecological risk assessments use studies with warm freshwater fish, cold freshwater fish, and estuarine/marine fish to assess acute risks to fish.
- Question: Is there a consistently more sensitive fish across all compounds and can we reduce data sets to two or even one fish study?
- Collaboration with NICEATM
- Status: QA of dataset on-going





# Case Study Using a NAM to Refine Inhalation Risk Assessment for Point of Contact Toxicity

- Case study with the pesticide chlorothalonil, which is a respiratory contact irritant
- Collaborated with Office of Pollution Prevention and Toxics (OPPT) and NICEATM
- Use of in vitro methods in conjunction with computational fluid dynamic (CFD) modeling as alternative to repeat dose inhalation study with laboratory animals
- First time a point of departure for risk assessment would be derived using in vitro data for a pesticide
- The meeting minutes and final report are now publicly available on the [www.regulations.gov](http://www.regulations.gov) docket at: [EPA-HQ-OPP-2018-0517](https://www.regulations.gov/docket/EPA-HQ-OPP-2018-0517)



# Continued Progress for Inhalation Alternatives

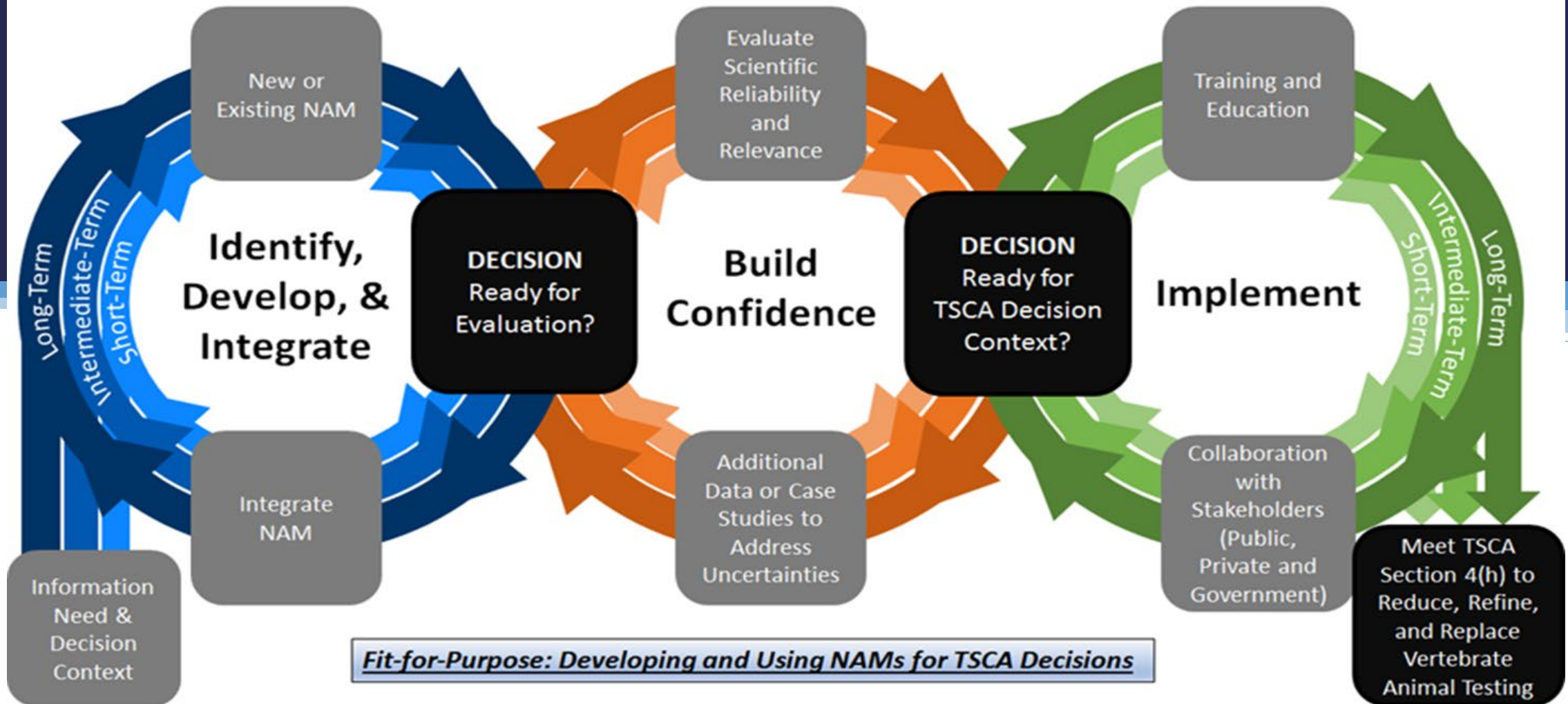
- ORD Research Project
  - Proof-of-concept study exposing commercially available 3D human lung culture models and 2D human primary bronchial epithelial cells at air-liquid interface
  - Chemicals nominated by OCSP, including known irritants
  - Evaluation of transcriptomic data and functional biomarkers (cell viability, barrier integrity)
- NIEHS Phase 2B grant:
  - Validation of a human airway epithelial model for identifying acute toxicity
  - Steering committee comprised of ICCVAM agencies (NIEHS, DoD, EPA, CPSC)
  - Lead laboratory (Mattek) and 2 additional laboratories to assess relevance and reliability
- PETA-ISC: Case study with a phased approach using increasingly more complex *in vitro* systems using silanes
- Working with industry to refine particle size information for use in pesticide exposure assessment

# Progress Report on Implementing Section 4(h) of TSCA: Reduction of Testing in Vertebrate Animals - OPPT



# Progress Report on Implementing Section 4(h) of TSCA: Reduction of Testing in Vertebrate Animals

Fig. 1 Core Components of EPA Strategic Plan to Develop and Implement New Approach Methodologies (NAMs) in TSCA



## List of NAMs, PEP Webinars

Maintain and Regularly Update a List of NAMs per Section 4(h)(2)(C)

- First list published on June 22, 2018
- First update scheduled in June 2019
- Draft document proposing a process to identify/nominate NAMs for listing is under development and will be released for public comment

Established a regular series of webinars (both internally for education/training and externally with stakeholders) and improve outreach/external engagement

- PETA/EPA/PCRM (PEP) webinars in place every other month (November 7, 2018; February 14, 2019; April 24, 2019)

## Building the TSCA Foundation of Information

- Identify and Maintain a List of Most Requested/Needed Studies for New and Existing Chemicals Under TSCA – Retrospective Analysis
- Identify and Curate Available Existing TSCA Information on NAMs (and Traditional Test Data) – CBI; TSCA In-House Inventory Analysis
  - These activities were combined into a single project
  - Work is progressing and anticipate public release in summer 2019
  - We are analyzing requested, required, and available data across human health, ecological toxicity, environmental fate, and physical-chemical properties
  - The data is anticipated to be broken into TSCA [New Chemical Categories](#) and [ECOSAR](#) categories, as well as exploration of new methods for chemical clustering.

## TSCA Implementation: Developing an IT Platform

- Deploying IUCLID 6.3 for managing chemical data.
- Deployed QSAR Toolbox 4.3 on CBI LAN environment to enable OPPT to better characterize hazard in the new chemicals program
- Collaborating with ECHA and Canada to:
  - Exchange public chemical data via IUCLID cloud instance
  - Identify approaches to enhance data exchange across jurisdictions
  - Identify opportunities to extend and enhance IUCLID and OECD Harmonization Templates
- Developed “sandbox” system on CBI LAN to test/use new tools for new (and existing) chemical assessments



Questions?