Progress on Implementing the TSCA Alternatives Strategic Plan

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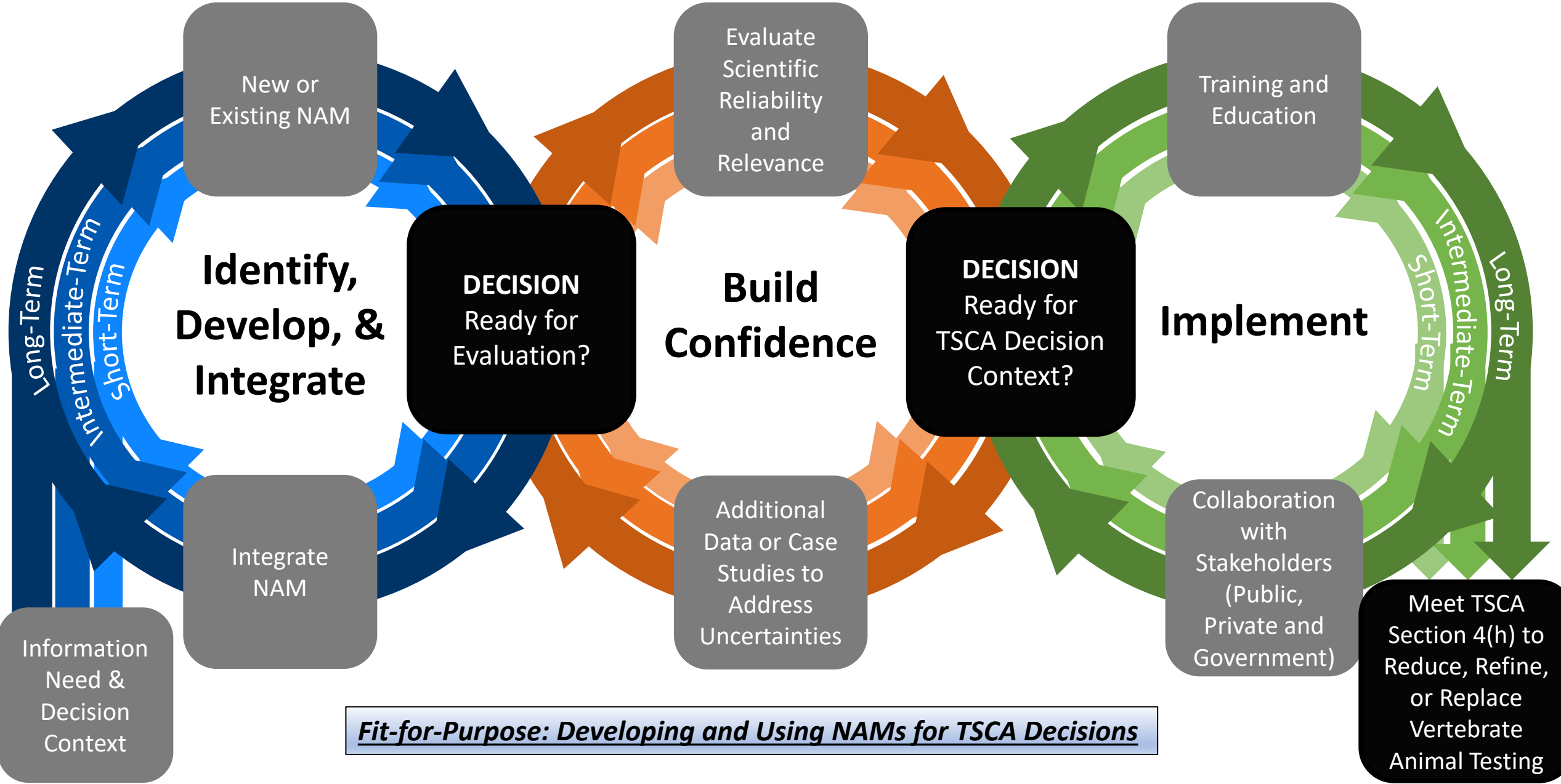
Disclaimer: The views expressed in this presentation are those of the presenter and do not represent Agency policy or endorsement. Mention of trade names of commercial products should not be interpreted as an endorsement by the U.S. Environmental Protection Agency.

The Toxic Substances Control Act (TSCA): The Frank R. Lautenberg Chemical Safety for the 21st Century Act 2016 Amendments

- A new Section 4(h) entitled: *Reduction of Testing on Vertebrate Animals*
- TSCA Section 4(h)(2) - ***Implementation of Alternative Testing Methods***—To promote the development and timely incorporation of new scientifically valid test methods and strategies that are not based on vertebrate animals**…**

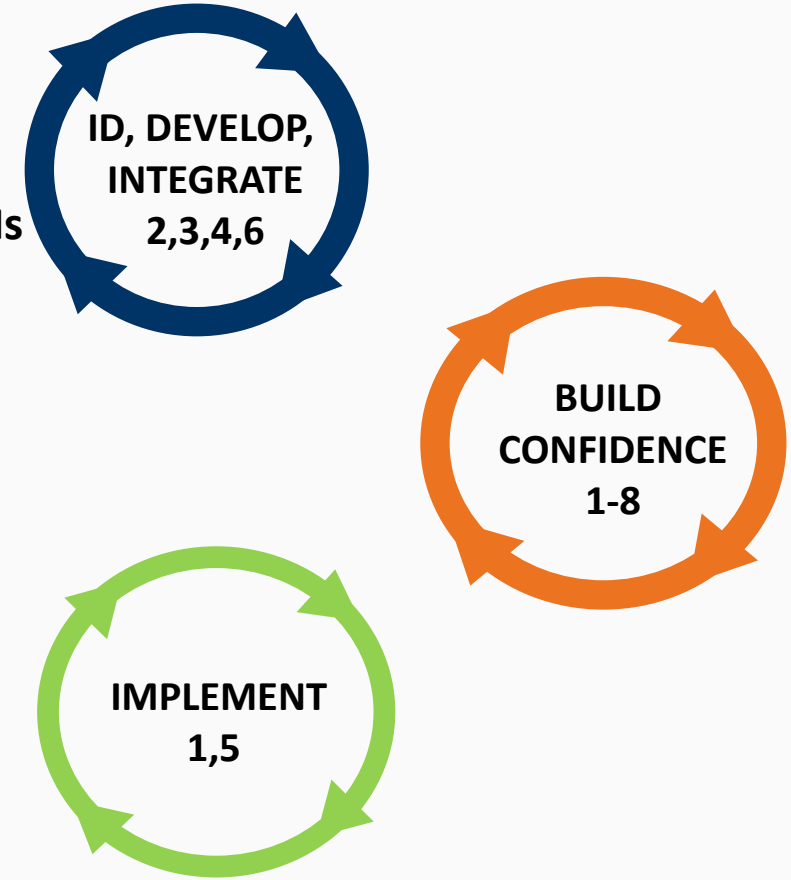
Fig. 1 Core Components of EPA Strategic Plan to Develop and Implement New Approach Methodologies (NAMs) in TSCA



Fit-for-Purpose: Developing and Using NAMs for TSCA Decisions

Progress on Eight Objectives in the Strategic Plan

1. **Implementation of NAMs (Two Examples):**
   - **Lung Effects Project**
   - **Skin Sensitization Project**
2. **Maintain and Update Section 4(h)(2)(c) List of TSCA Acceptable NAMs**
   - **Original List (June 2018) and First Update (December 2019)**
   - **TSCA NAM Nomination Form/Process**
3. **Identify TSCA Information: Retrospective**
   - **What we have asked for and expect to receive**
4. **Identify TSCA Information: Available CBI**
   - **What we have received**
5. Use of NAMs for Prioritization
6. Development of IT Platform
7. Collaborate with Partners
8. Launch TSCA NAM Website



1. Implementing NAMs: Lung Effects Example*

- EPA New Chemical Categories Document
  - *https://www.epa.gov/sites/production/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf*
- Lung Effects Categories/Examples of Tiered Testing:
  - Poly-cationic substances (cationic binding)
  - Surfactants
  - Waterproofing
  - Insoluble polymer lung overload

** Slides adapted from OPPT presentation to ICCVAM RAWG in February 2020 and manuscript submitted to Chemical Research in Toxicology in July 2020*

Lung Overload Definition*

"This is defined as the overwhelming of macrophage-mediated clearance by the deposition of particles at a rate which exceeds the capacity of that clearance pathway. It is a nonspecific effect noted in experimental studies, generally in rats, using many different kinds of poorly soluble particles [PSPs] (including TiO_2, volcanic ash, diesel exhaust particles, carbon black, and fly ash) and results in A [alveolar] region clearance slowing or stasis, with an associated inflammation and aggregation of macrophages in the lungs and increased translocation of particles into the interstitium."

*EPA (1996) *Air quality criteria for particulate matter, Volume II of III*, Office of Research and Development, U.S. Environmental Protection Agency (EPA), EPA/600/P-95/001bF, 774 pp., at p. 10-71 (pdf p. 314).

Insoluble Polymer Lung Overload Category Boundaries for TSCA Purposes*

1. Respirable particles are considered those with an aerodynamic diameter less than or equal to 10 µm and are present at greater than or equal to 1 percent by weight (wt%);
2. Non-reactive particles are those that meet EPA's exemption (E) criteria for functional groups and functional group equivalent weight for E1 polymers; and
3. Poorly soluble polymers are those that are water extractable at less than 100 mg/L or have solubilities less than 100 mg/L in artificial alveolar fluid or less than 1 mg/L in artificial lysosomal fluid.

**The boundaries for polymers with molecular weights ≥10,000 Daltons include those that do not meet the exclusion criteria listed under EPA's polymer exemption at 40 CFR § 723.250(d)*

Polymer Lung Overload: Proposed Tiered Testing

Tier I – Particle size distribution/aerosolized droplet size, Reactivity, and Biosolubility testing

- If the % of respirable particles (*i.e.*, ≤ 10 µm) is > 1 wt%, the polymer is non-reactive, and has a dissolution rate that is lower than the estimated daily occupational exposure estimate, proceed to Tier II.

Tier II – Perform computational modeling (*e.g.*, MPPD) to predict deposition, clearance, and lung burden for a simulated chronic rat exposure.

- If the simulations indicate overload under the conditions of use, consider risk management options (*e.g.*, engineering controls and personal protective equipment) or proceed to Tier III.

Tier III – Strategic *in vivo* testing should be considered, albeit on a case-by-case basis, and after discussions with EPA at a pre-notice consultation meeting.

Recent Application of Lung Effect NAMs – SNUR Revocation

Federal Register / Vol. 85, No. 165 / Tuesday, August 25, 2020 / Rules and Regulations

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Parts 9 and 721

[EPA–HQ–OPPT–2017–0575; FRL–10012–90]

RIN 2070–AB27

Revocation of Significant New Use Rule for a Certain Chemical Substance (P–16–581)

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

Federal Register / Vol. 85, No. 63 / Wednesday, April 1, 2020 / Proposed Rules

The biosolubility testing was conducted using a conservative respiratory tract fluid volume of 0.3 mL/kg bw (rounded down to 20 mL for a 70 kg individual). This equated to a loading concentration of 15 mg of the PMN substance per mL of simulated epithelial lung fluid (SELF). The SELF represented the intraluminal volume of respiratory tract fluid, without consideration of the daily turnover volume. The estimated average alveolar fluid volume is approximately 37 mL, nearly double the volume used for the biosolubility testing. In comparison, the normal reference range for extra vascular lung water (EVLW) index in humans is 7.3 ± 2.8 mL/kg bw (n = 534) or 511 mL for a 70 kg individual. EVLW index corresponds to the "sum of

This information supports EPA's determination that the substance has inherently low toxicity and should not be considered a poorly soluble particle with the associated hazard concern for lung overload. Therefore, EPA proposes that the SNUR for this chemical substance be revoked pursuant to 40 CFR 721.185(a)(1).

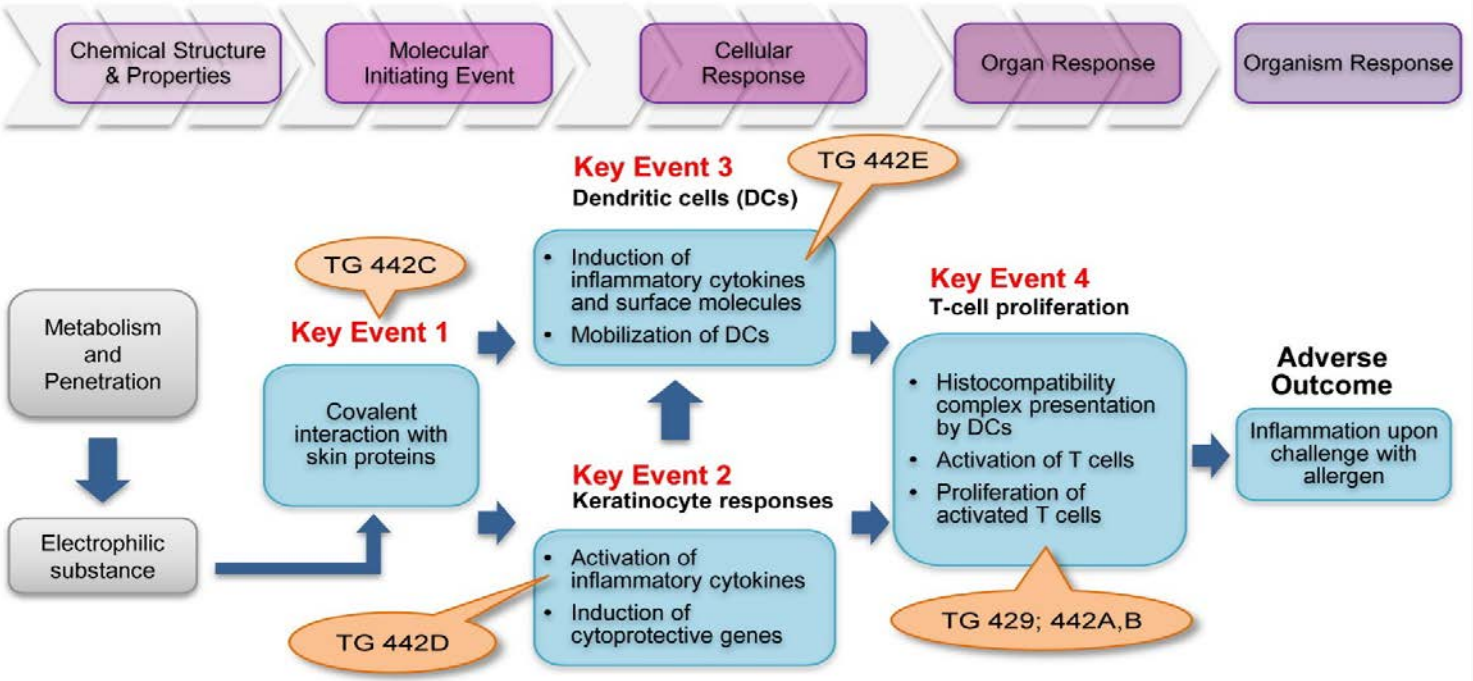
Implementing NAMs: Skin Sensitization Example

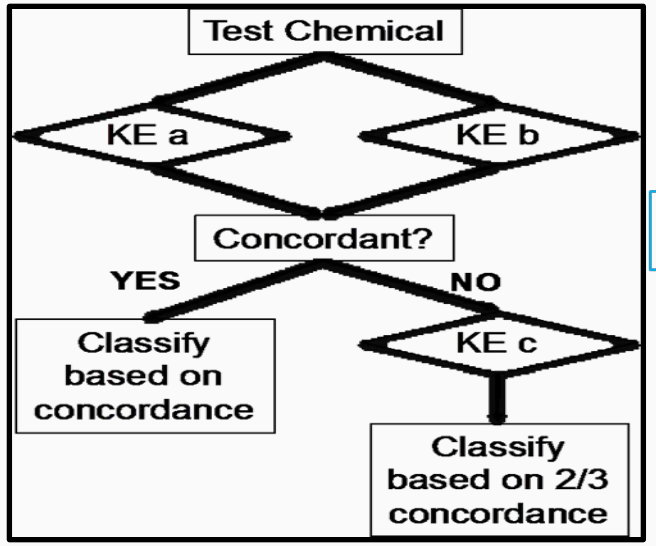
- OCSPP Policy*
  - AOP and Defined Approaches
- Skin Sensitization NAMs: Received by the OPPT New Chemicals Division
- Skin Sensitization NAMs: NICEATM Testing of 51 TSCA Chemicals

**Draft Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing*
https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0093-0090

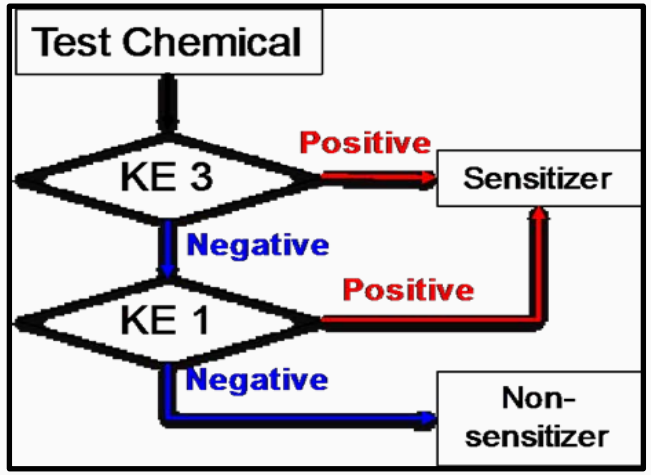
Adverse Outcome Pathway (AOP)

(adapted from Strickland et al., 2018)





"Two out of Three"



Key Event 3/1 Sequential Testing Strategy

Overview of Information OPPT Has Received (Non-CBI Information Presented)

- OPPT has received 49 submissions with skin sensitization NAMs from October 2015 to April 2020 as part of new chemical submissions
- The submissions were received from 24 different companies
- The work was performed by 16 different laboratories

Overview of Information OPPT Has Received (cont.)

Fiscal Year	Submissions with NAMs Only	Submissions with NAMs plus *in vivo*	Submissions with NAMs plus RIPT*	Submissions with NAMs, *in vivo,* and RIPT	Totals
2015	2	2	3	1	6
2016	5	2	5	2	10
2017	1	-	1	-	2
2018	3	6	2	1	10
2019	9	-	1	-	10
2020	7	4	1	1	11
Totals	**27**				**49**

*RIPT = Human Repeated Insult Patch Test

TSCA Chemicals Tested by NICEATM*

- 51 Substances
  - 43 LLNA positive
  - 7 LLNA negative
  - 1 Equivocal LLNA, described as “unclear”
- *In Vitro* Data
  - DPRA, KeratinoSens™, and h-CLAT conducted under contract to NTP
  - Inconclusive results: 3 for DPRA (LLNA positive), 4 for KeratinoSens (LLNA positive), and 0 for h-CLAT
  - No results: 3 for DPRA, 4 for KeratinoSens, and 4 for h-CLAT
- LLNA Data
  - LLNA provided by OPPT: ECETOC potency category, additional information was variably reported (EC3, concentrations tested, vehicle, SI, sponsor)

** Slide adapted from NICEATM/ILS presentation to OPPT on August 14, 2020*

2. Maintain and Update List

- The List
  - Original (June 2018)
  - First Update (December 2019)
- NAM Nomination Process

TSCA Section 4(h)(2)(c) List

Original (June 2018) List

NAMs Listed (Four Tables)

- Table 1 (23): OECD TG – HH
- Table 2 (6): OECD TG – Biotic Sys.
- Table 3 (1): EPA Policies
- Table 4 (9): EPA-Specific NAMs (TSCA)
- TOTAL = 39

First Update of List (December 2019)

NAMs Listed (Five Tables)

- Appendix A: (Four Tables)
  - 30 + 19 + 7 + 10 = 66
- Appendix B: (One Table [19])
- TOTAL = 85

From the OPPT NAM Website

2. Maintain and regularly update a list of NAMs per TSCA Section 4(h)(2)(C)

- EPA published a list of NAMs in June of 2018 and committed to updating the list at least once a year. The first update was released in December 2019. *Additionally, EPA plans to release a draft proposal on a process for selecting which NAMs will be included on future versions of the list. This draft proposal will be released for public comment in 2020.*

So, How Does a NAM Get on the TSCA List?*

- There are organizations/entities that evaluate and "approve" NAMs (*e.g.,* OECD Test Guideline Program, ICCVAM, ECVAM)
- But there may be other NAMs useful for TSCA decisions
- During 2020, EPA will propose suggestions on how NAMs could be considered for inclusion in the TSCA Section 4(h)(2)(c) List

**Slides adapted from PEP Webinar on September 30, 2020 (Simmons, US EPA/ORD)*

Practical Goals for NAM Nomination

Get lots of good NAMs added to the list

1. Encourage NAM nominations from a diversity of sources
2. Provide guidance on what EPA wants from a NAM for TSCA
   - How might we use it? What are the risk decision scenarios under TSCA?
   - What do we need for it to be usable? How do those differ by scenario?
   - What are the minimal performance criteria for acceptance/use?

What does the "Perfect NAM Nomination" Look Like?

- Method does not rely upon intact animals
- Provides relevant data that seamlessly integrates in TSCA regulatory activities:
  - Risk assessment (screening-level) of new chemicals
  - Prioritization of existing chemicals
  - Risk evaluation of existing chemicals
- Provides quantitative data
- Covers the diversity of TSCA chemical space
- Highly predictive of known values (ground-truthing)
- Reproducible
- Transferrable/Accessible
- Transparent

Who Might Nominate a NAM for TSCA Use?

- U.S. EPA
- Other U.S. Federal Agencies
- International Agencies
- Groups advancing alternatives to animal tests
- TSCA submitters (regulated industry)
- Consulting firms specializing in TSCA support
- Companies with assays, models, and other tools seeking to repurpose and commercialize for TSCA compliance

NAM sources will have differing expertise, incentives, and familiarity with TSCA

NAM Nominations - a Distillation

- What are the Critical Elements for a Nomination?
  - Nominal Information
    - What is it?
  - Development History
    - How was it developed and by whom?
  - Method Description
    - How does it work? What are the steps involved?
  - Relevance
    - Does it predict anything useful for decisions about TSCA chemicals?
  - Reliability
    - Can we rely on the output and justify our decisions based on it use?

Decision Context

Endpoint ↔ Context

Chemical Coverage

Reference Chemicals

Reproducibility

Predictivity

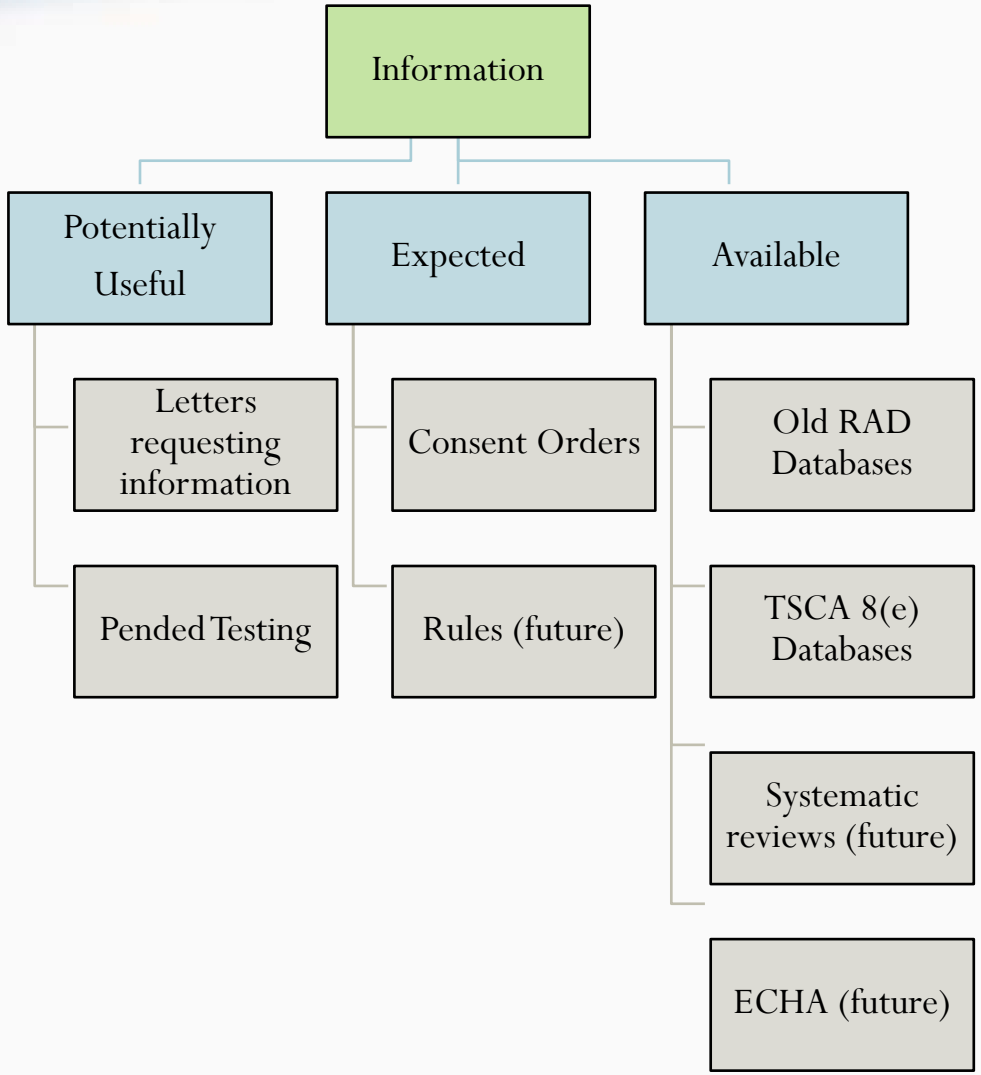
Transparency

3 and 4. Analysis of TSCA Available, Expected, and Potentially Useful Information (ATAEPI)

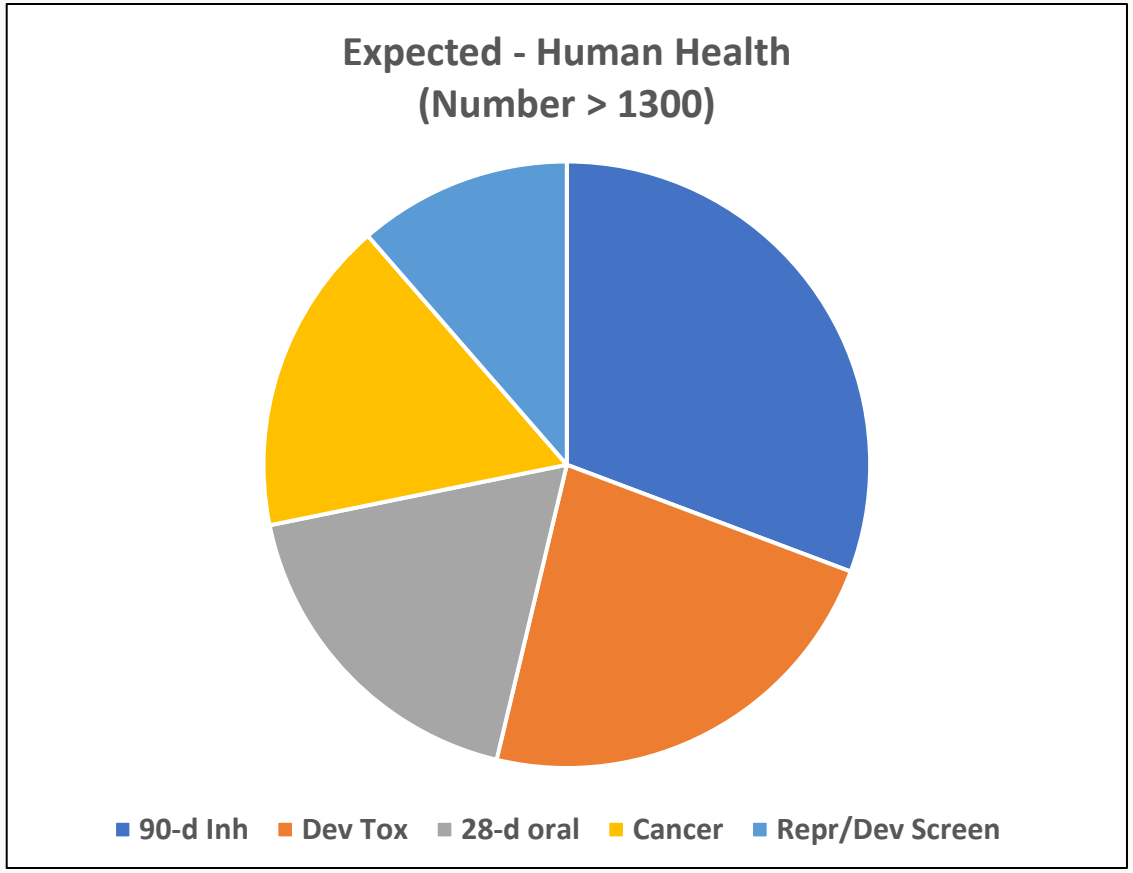
- ATAEPI addresses 3 of the 8 near-term objectives that require data science expertise:
  - **Retrospective Analysis**: Identify and Maintain a List of Most Requested/Needed Studies for New and Existing Chemicals Under TSCA
  - **TSCA In-House Inventory Analysis**: Identify and Curate Available Existing TSCA Information on NAMs (and Traditional Test Data) – CBI
  - Support the build out of the **Scientific Information Technology Platforms** to better integrate information from multiple databases related to chemical submissions.

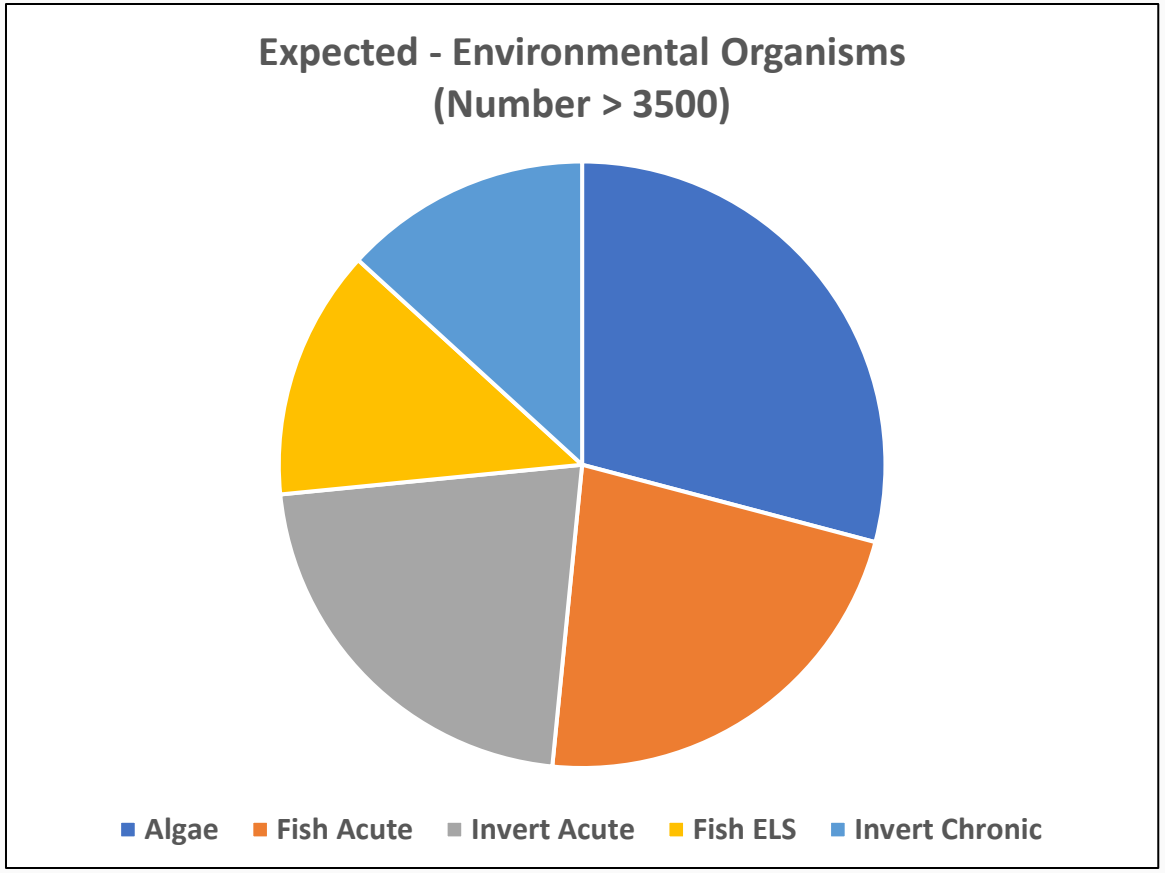
ATAEPI Overview

- Information on the human health and ecological hazards, environmental fate, and physical-chemical properties captured.
- Analysis includes all new chemical submissions since the first one in 1979.

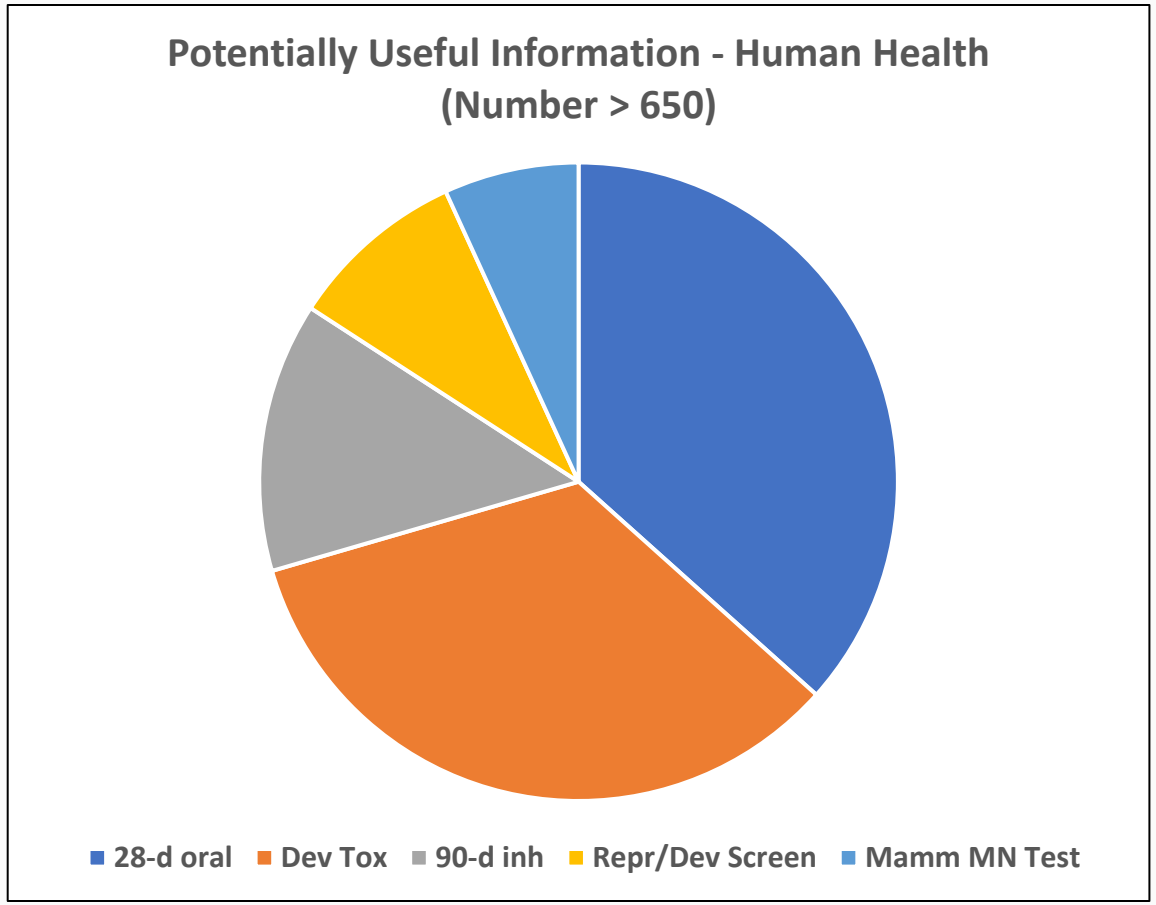


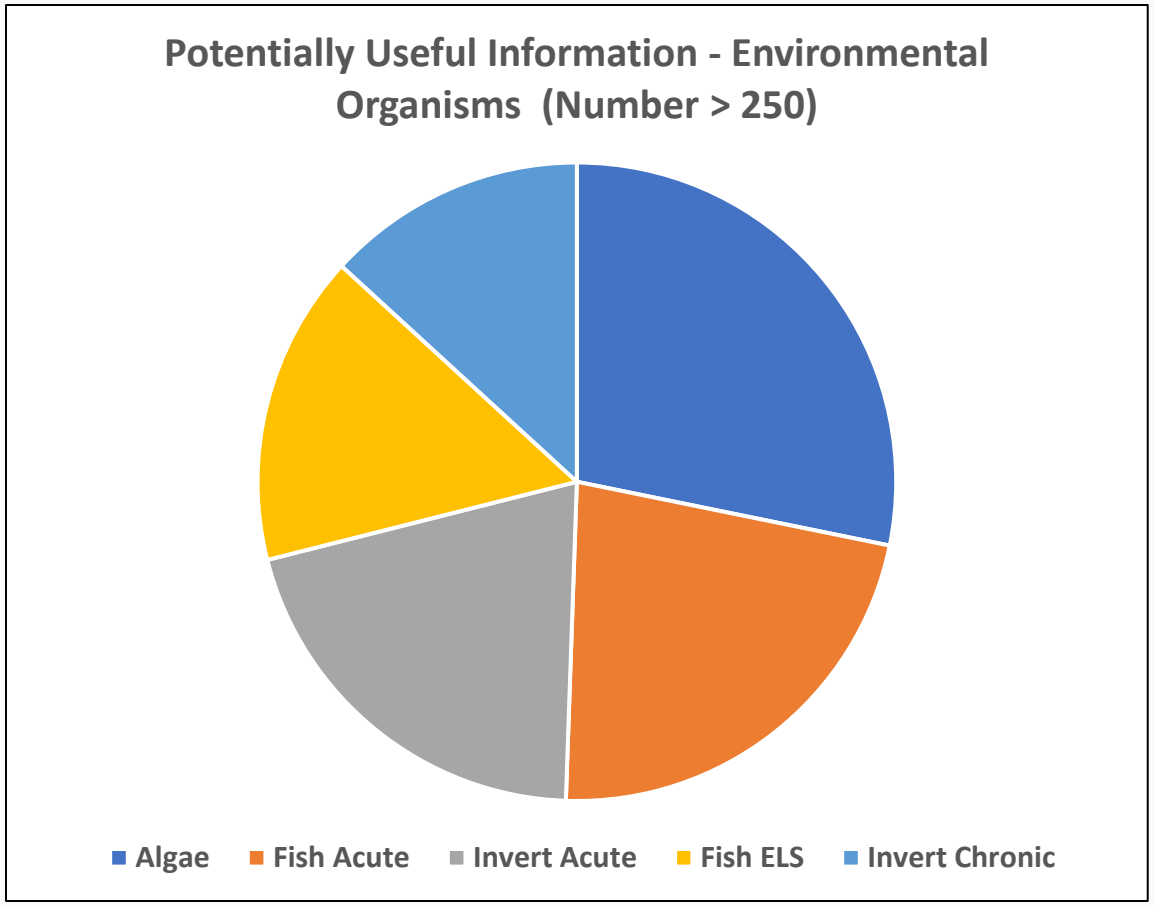
Preliminary Numbers for “Expected”





Preliminary Numbers for “Potentially Useful”





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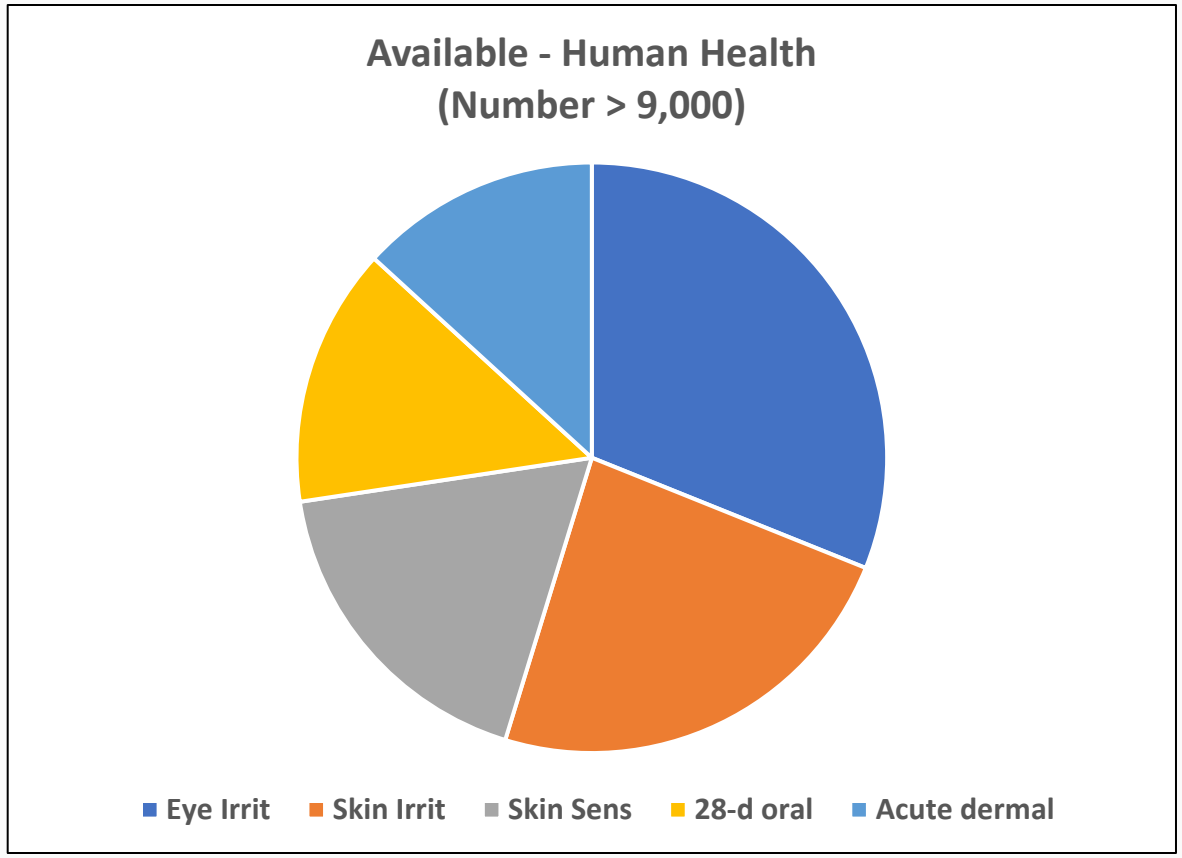

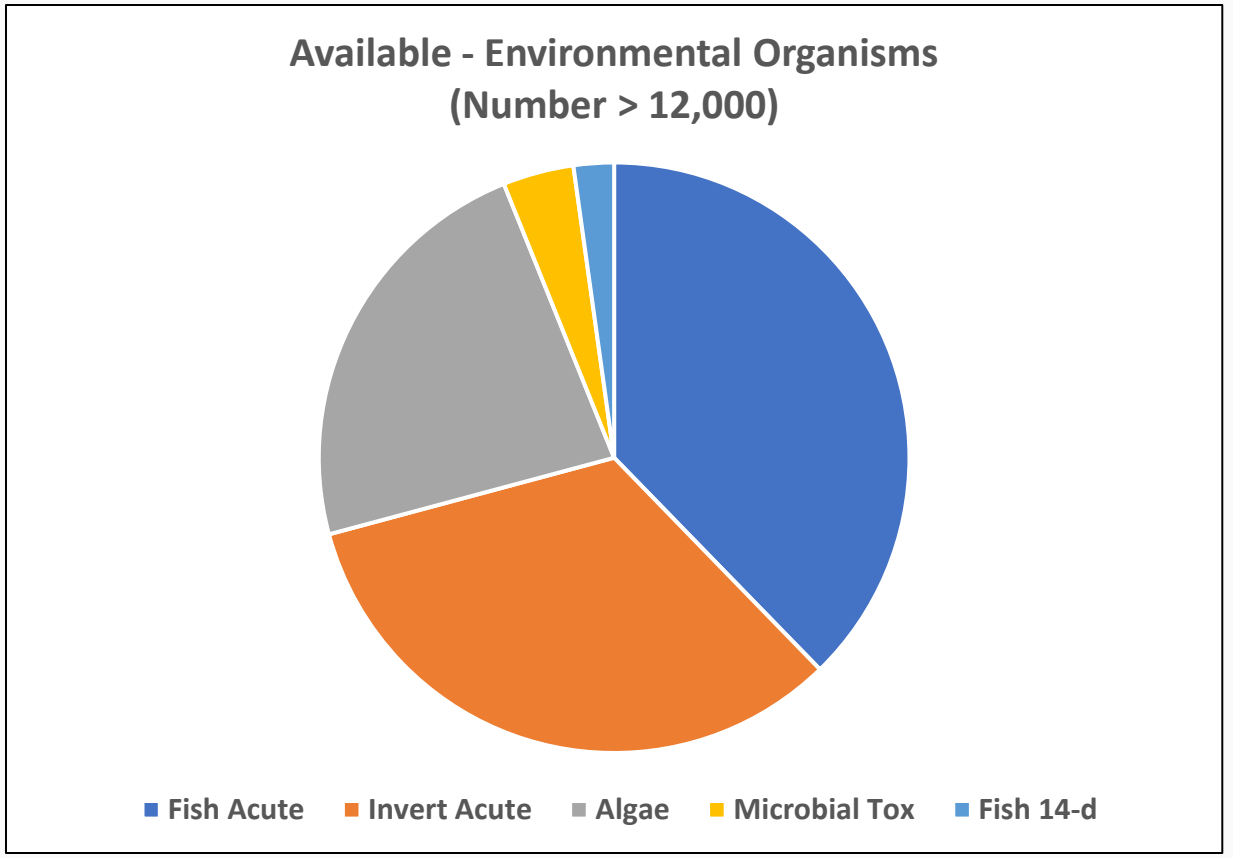

5. Use of NAMs to Identify Candidates for Prioritizing Existing Chemicals for TSCA Risk Evaluation

OPPT recently reorganized and there is a new Division dedicated to this effort: the **Data Gathering and Analysis Division (DGAD). The new Division has two Prioritization and Informatics Branches.*

6. Develop an IT Platform

- Deploying IUCLID 6.3 for managing chemical data
- Deployed OECD QSAR Toolbox 4.3 on CBI LAN environment
- 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

7. Collaborate with Partners and Stakeholders to Identify NAMs for Further Development

- Established a regular series of webinars – both internally for education/training and externally with stakeholders:

  - PETA/EPA/PCRM (PEP) webinars – seven so far; please see: https://www.piscltd.org.uk/nam-webinars/

- ICCVAM and OECD activities/workgroups

- Academic, industry, and stakeholder exchanges

Next Steps….

1. Implementation of NAMs
   - Lung Effects Project – Starting to implement approach, two manuscripts submitted, other lung effects subcategories being worked on
   - Skin Sensitization Project – Internal review continuing, NICEATM helping with TSCA analysis (and other DAs), monitoring OECD activity
2. Maintain and Update Section 4(h)(2)(c) List of TSCA Acceptable NAMs
   - Original List (June 2018) and First Update (December 2019) – Second Update by end of calendar year
   - TSCA NAM Nomination Form/Process – Nomination form tested by contractor, form and process to be publicly released 2020 (maybe early 2021)
3. Identify TSCA Information: Retrospective
4. Identify TSCA Information: Available CBI

ATAEPI work continuing….

5. Use of NAMs for Prioritization – New Division dedicated to this effort!
6. Development of IT Platform – Also part of new Division!
7. Collaborate with Partners – Continuing!
8. Launch TSCA NAM Website – DONE

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THANK YOU!