# Application of New Approach Methodologies to Chemical Assessment and Regulatory Decision-Making: The Importance of an International and Harmonized Effort

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SOT Workshop:
Regulatory Learnings from the EU Flagship
Non-animal Toxicology Project, EU-ToxRisk

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# Conflict of Interest Statement

*The author declares no conflict of interest.*

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# Outline

- New Approach Methods
- Increasing Translation
- Harmonization effort examples:
  - EUToxRisk
  - OECD Environmental Health and Safety Programme
  - Accelerating the Pace of Chemical Risk Assessment
- Benefits of International Collaboration
- Continued Goals
- Acknowledgements


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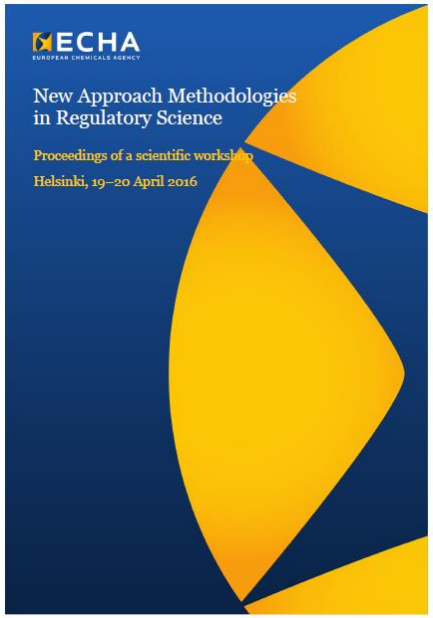
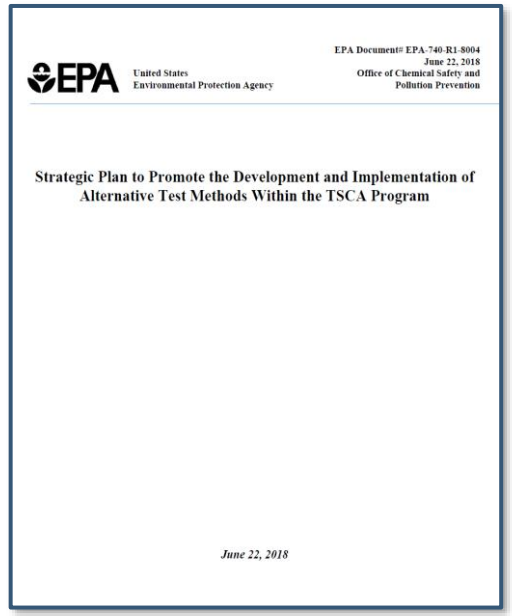
# Definition(s) of New Approach Methods (NAMs)




- Commonly defined to include in silico approaches, in chemico and in vitro assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard and exposure assessment.

- Defined in the EPA's TSCA Alternative Toxicity Strategy as:
  - a broadly descriptive reference to any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals.


EPA Document# EPA-740-R1-8004
June 22, 2018
Office of Chemical Safety and Pollution Prevention

EPA United States Environmental Protection Agency

Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program

June 22, 2018

https://echa.europa.eu/documents/10162/22816069/scientific_ws_proceedings_en.pdf

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce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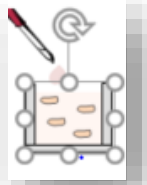
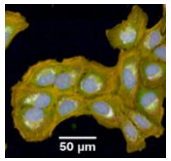
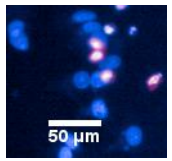
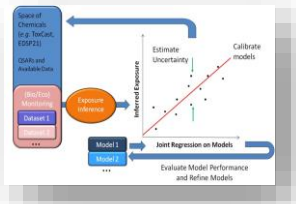
# Examples of New Approach Methods

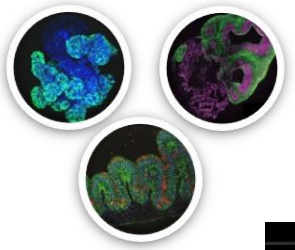


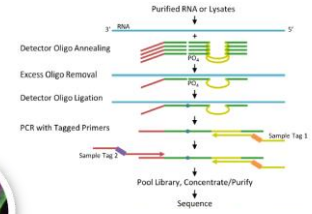


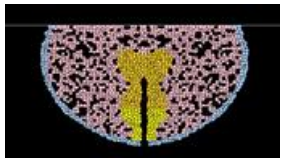




- In silico (e.g. QSAR and Read-across)
  - Estimate effects and doses
  - Consensus exposure modeling
- In vitro assays
  - Broad / screening (transcriptomics, cell painting)
  - Targeted (receptors, enzymes)
  - In vitro PODs, modes / mechanisms of action
- In vitro Toxicokinetics
  - Allow conversion of an in vitro POD to in vivo (IVIVE)
- High-throughput Exposure Measurements
  - To fill data gaps in monitoring data
- Computer models
  - Hazard models to integrate multiple in silico and in vitro data streams
  - Exposure models to increase information on different pathways of exposure



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# What is needed for increased translation of NAMs for regulatory decisions?

- Common understanding of current state of the science of NAMs, including the application in a regulatory context.
- Increase understanding of realistic benchmarks for performance of NAMs in different regulatory contexts.
- Increase engagement and commitment to development and sharing of case studies of mutual interest.
- Increase collaboration to strategically address barriers and limitations of use of NAMs in a regulatory context.


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# Benefits of Collaboration

- Maximizing shared resources
- Benefitting from shared lessons learned
- Filling data gaps of common concern
- Engaging broader range of stakeholders
- Increasing understanding of NAMs applications


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# Example 1: EU-ToxRisk

- An Integrated European ‘Flagship’ Programme Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st century.
- Began in 2016 and funded from the European Union’s Horizon2020 research and innovation program.
- Aim was to develop the tools and strategies that will enable reliable animal-free risk assessment of chemicals.
- Further aim to increase close interaction among researchers and regulators to significantly improve targeting regulatory needs, thereby enhancing the societal impact of the project.



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# Example 1: EU-ToxRisk Lessons Learned

- Main areas already discussed today:
  - Importance of practical case studies
  - Need for data sharing framework and data integration across case studies
  - Establishing a good regulatory reporting practice for NAMs (e.g., NAM-enhanced read-across)
  - Need to share with the international community to promote sustainability of the approach



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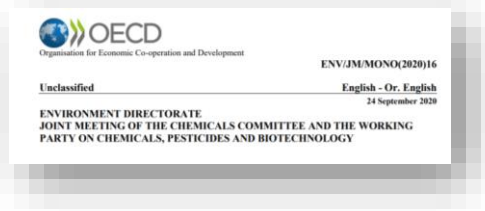
# Example 1: EU-ToxRisk Impact

- Utilization of international discussion platforms for promoting the implementation of NAMs, mostly focused on NAM-enhanced RAx via:
- **F2F meetings**, harvesting the collective experience of those developing and applying RAx approaches with NAMs to coordinate the ongoing opportunities and challenges in assuring scientific confidence in their use;

- **Publications**, internationally promoting the regulatory implementation of NAM-based RAx, i.e. the EU-ToxRisk CS reports published by the IATA Case Studies Project.

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EUTOXRISK

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# Example 2: OECD ENVIRONMENT, HEALTH AND SAFETY (EHS) DIVISION

38 Member Countries, many partner countries and other stakeholders work together to develop and co-ordinate activities on chemical safety and biosafety on an international basis. One of the core aspects of the work relates to the Mutual Acceptance of Data.

The main objectives of EHS are to:

- Assist OECD Member countries' efforts to protect human health and the environment through improving chemical safety and biosafety;
- Make chemical control policies more transparent and efficient and save resources for government and industry; and
- Prevent unnecessary distortions in the trade of chemicals, chemical products and products of modern biotechnology.

http://www.oecd.org/env/ehs/


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# Example 2: OECD Methodologies for Hazard Assessment

- Works with member countries and other stakeholders to cooperatively assess the hazard of chemicals
  - Tools and information are publicly available
  - Can be used for priority setting, risk assessment, and other activities
  - Improve and harmonize chemicals assessment methods using the most current science
  - Generate confidence and support for integrating novel tools and approaches into regulatory decision-making

- Types of Output:
  - Guidance Documents and case studies using novel methods for regulatory decision-making
  - Adverse Outcome Pathways Knowledge Base
  - QSAR Toolbox
  - Integrated approaches to testing and assessment (IATA)

http://www.oecd.org/env/ehs/risk-assessment/

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# Example 2: OECD – Integrated Approaches to Testing and Assessment (IATA) Case Studies Project

- Objective:
  - Increase experience with the use of IATA by developing case studies, which constitute examples of predictions that are fit for regulatory use
  - Provide a scientific exchange on how novel methods are applied to assess the hazard of chemicals
  - Establish a common understanding and best practices for using novel methodologies in a regulatory context
- Deliverables:
  - Guidance documents on methodologies with associated case studies
  - Lessons learned/considerations from each IATA case study project cycle

http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm

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# Example 2: OECD – IATA Case Studies Project

| Review Year | Title | Endpoint | Status |
|---|---|---|---|
| 2020 | Case Study on the use of Integrated Approaches for Testing and Assessment for the Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion | Repeated toxicity | Under Review |
| 2019 | Case Study on the use of an Integrated Approach to Testing and Assessment (IATA) and New Approach Methods to inform a Theoretical Read-Across for Dermal Exposure to Propylparaben from Cosmetics | Reproductive toxicity | Published |
| 2019 | Case Study on the use of Integrated Approaches for Testing and Assessment for Systemic Toxicity Arising from Cosmetic Exposure to Caffeine | Repeated dose toxicity | Published |
| 2019 | Case Study on the Use of Integrated Approaches for Testing and Assessment for 90-Day Rat Oral Repeated-Dose Toxicity of Chlorobenzene-Related Chemicals | Repeated dose toxicity | Published |
| 2019 | Case Study on the Use of Integrated Approaches for Testing and Assessment to Inform Read-across of p-Alkylphenols: Repeated-Dose Toxicity | Repeated dose toxicity | Published |
| 2019 | Prediction of a 90 day repeated dose toxicity study (OECD 408) for 2-Ethylbutyric acid using a read-across approach from other branched carboxylic acids | Repeated dose toxicity | Published<br>Annex III |
| 2019 | Read-across based filling of developmental and reproductive toxicity data gap for methyl hexanoic acid | Developmental toxicity | Published<br>Annex II<br>Annex III |
| 2019 | Identification and characterisation of parkinsonian hazard liability of deguelin by an AOP-based testing and read across approach | Neurotoxicity | Published<br>Annex I |
| 2019 | Mitochondrial Complex-III-mediated neurotoxicity of - Read-Across to other strobilurins | Neurotoxicity | Published<br>Annex I |
| 2018 | Case Study on the use of Integrated Approaches for Testing and Assessment for Testicular Toxicity of Ethylene Glycol Methyl Ether (EGME)-Related Chemicals | Reproductive toxicity | Published |
| 2018 | Case Study on the Use of an Integrated Approach to Testing and Assessment for Identifying Estrogen Receptor Active Chemicals | Endocrine disruption | Published |

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# Example 3: Accelerating the Pace of Chemical Risk Assessment

An international governmental collaboration that brings together governmental entities engaged in development of new hazard, exposure, and risk assessment methods and approaches for their chemical evaluation activities.


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- To discuss progress and barriers in applying new tools to prioritization, screening, and quantitative risk assessment of differing levels of complexity.
- To discuss opportunities to increase collaboration through case studies in order to accelerate the pace of chemical risk assessment.

https://www.epa.gov/chemical-research/accelerating-pace-chemical-risk-assessment-apcra

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# Example 3: APCRA Intergovernmental Collaborative Case Studies

- Case studies developed address the following criteria:
  - Common issue for more than one regulatory partner (e.g., PFAS)
  - Active engagement for more than one regulatory partner
  - Supports clear regulatory context
- Case study topic areas
  - Application to Human Health and Ecological Risk Evaluation
  - Application to Chemical Categorization
  - Application to Exposure Evaluation

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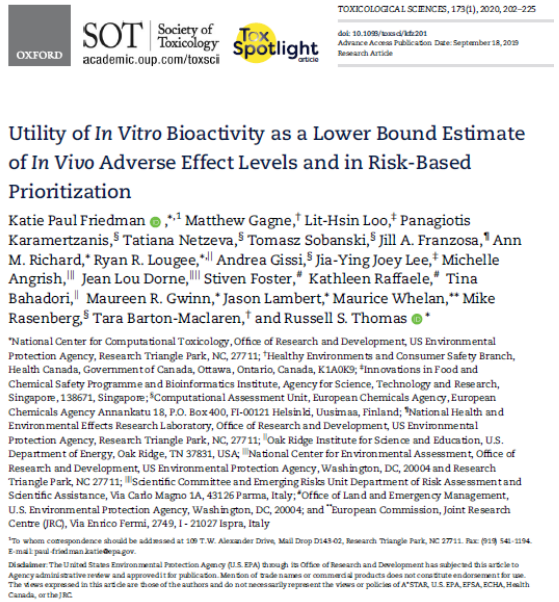
# Example 3: APCRA Completed Case Studies



OXFORD | SOT Society of Toxicology academic.oup.com/toxsci | Tox Spotlight

TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225
doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

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- Retrospective Case Study Examining the Utility of In Vitro Bioactivity as a Conservative Point of Departure
  - Leads: US EPA and Health Canada
  - Partners: EChA, EFSA, A*STAR

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- Linking Exposure to Toxicology Using Lead as Case Study
  - Lead: US EPA
  - Partners: EFSA, CalEPA, INERIS

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Toxicol Sci. 2019 doi: 10.1093/toxsci/kfz201

# Benefits of International Collaborations

- Platforms for innovation and idea exchange between a broader range of stakeholders
- Lead discussions on when there is sufficient knowledge and confidence to bring NAMs into particular regulatory contexts
- Continue to develop new collaborative case studies to address gaps in common scientific and regulatory needs
- Sharing resources and lessons learned
- Increase regulatory confidence in NAMs


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# Continued Goals

- Continued increased understanding of NAMs
- Building scientific confidence
- Expand translation of NAMs
- Increased implementation in risk assessment and regulatory decisions
- Create a potential pipeline from sharing information to developing harmonized approaches, results of which may be covered under mutual acceptance of data under OECD


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