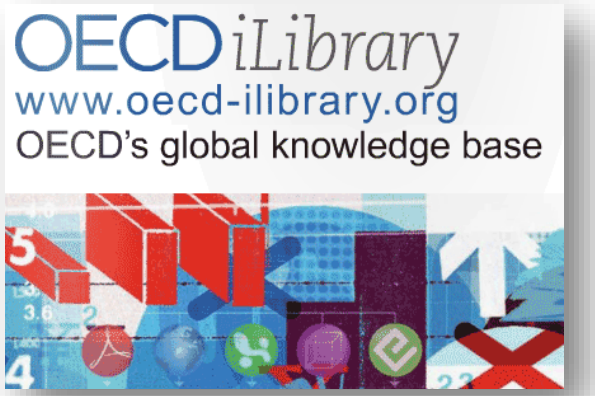
GAINING CONFIDENCE IN THE USE OF NEW APPROACH METHODS THROUGH INTEGRATED APPROACHES TO TESTING AND ASSESSMENT

Bob Diderich, OECD, September 2023

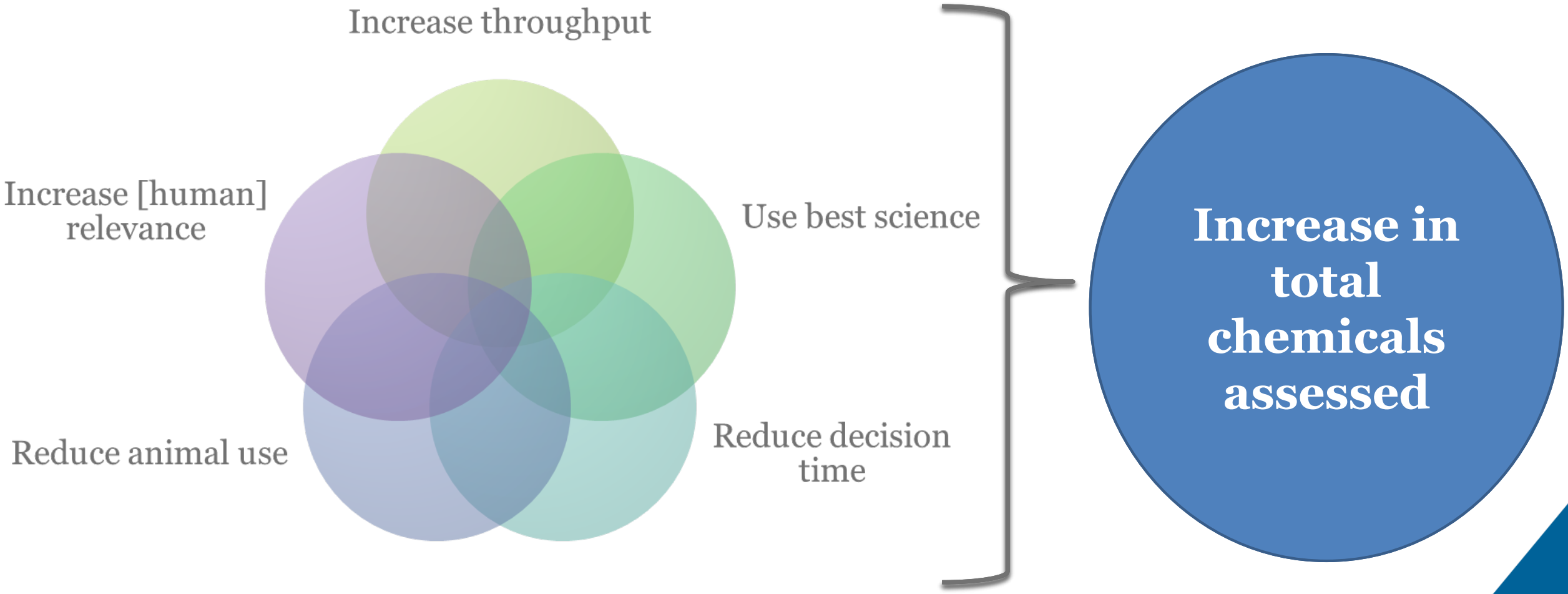
OECD Chemical Safety Programme

Is a forum for governments and other stakeholders to:

- Develop methods and approaches for evaluating the safety of chemicals
- Discuss and share their experiences on issues of mutual concern;
- Promote harmonized approaches and data sharing
- Increasing focus on the use of New Approach Methods



Global drivers to modernise chemical risk assessment



OECD Test Guidelines and Mutual Acceptance of Data -> Increased capacity for risk assessment globally

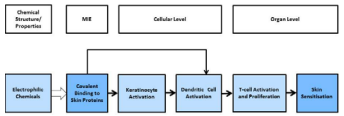
- Results of OECD internationally harmonised Test Guidelines conducted according to Principles of Good Laboratory Practice are covered by Mutual Acceptance of Data
  - Reduces costs of chemical testing for governments and industry
    - Monetary savings of 309 MEUR per year: https://www.oecd.org/environment/saving-costs-in-chemicals-management-9789264311718-en.htm
  - Increases the number of chemicals that can be tested globally
    - If each industry/government/lab can only perform X tests per year, Mutual Acceptance of Data increases the total number of chemicals tested globally

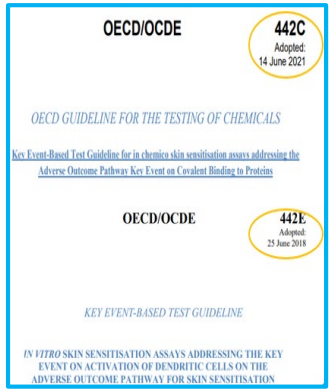
Test Guidelines Programme

- Most projects on OECD Test Guidelines Programme today are about harmonisation of non-animal methods
- Achievements include a number of harmonised TGs e.g.

  - skin and eye irritation/corrosion
    - associated Performance Standards
    - related Guidance Document on IATA

  - skin sensitisation
    - Underpinning AOP
    - IATA case studies
    - Key event-based TGs
    - Defined Approaches TG



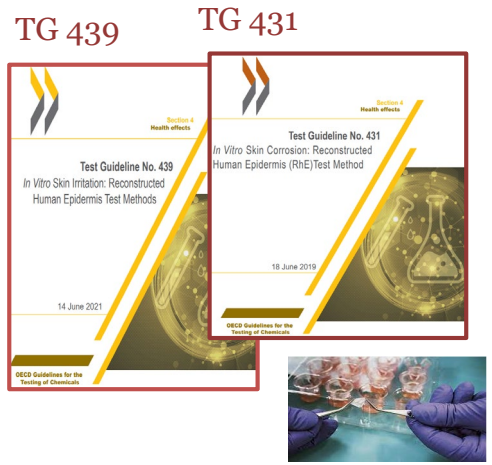


TG 442C

TG 442E

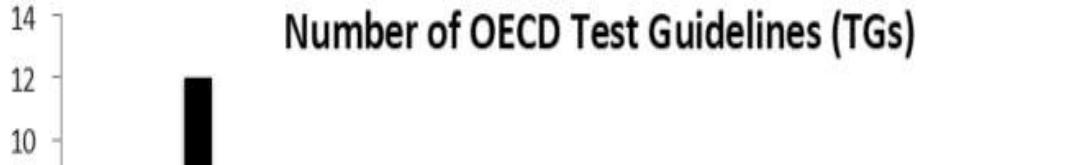
TG 497

TG 439 TG 431



TG 437 TG 438 TG 491 TG 492 TG 494 TG 496

Current number of Test Guidelines based on New Approach Methods



	acute systemic tox	repeated dose tox	mutagenicity/ genotoxicity	carcinogenicity	skin corr/ irrit	serious eye dam/ irrit	skin sensitisation	photo-induced tox	repro/ develop m tox	ADME/TK
■ In vivo TGs	7	12	8	2	1	1	4	0	8	2
□ In vitro/in chemico TGs	0	0	5	1	4	7	3	1	0	1

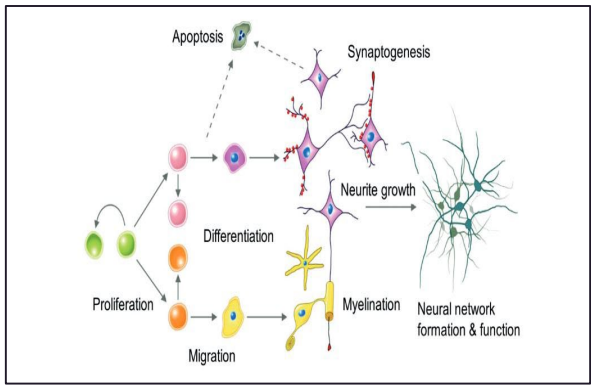
From Pistollato et al., 2021

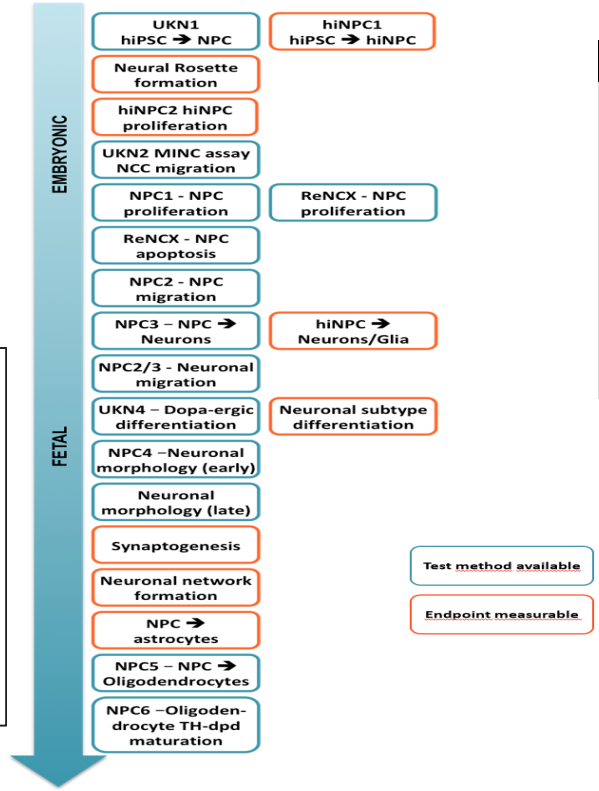
- ~35 NAM TGs
- 2 Defined Approaches
- Almost all focused on human health
- Most on simple endpoints and acute toxicity

Developmental Neurotoxicity

Guidance on use of an in vitro battery (IVB) of assays for DNT (EFSA-EC/DK/US)

EFSA/OECD WS (2017)





Readiness/ Test method	Phase I	Phase II	Phase III	Overall readiness
UKN1	A	B	B	B+
NPC1	A	A	A	A
NPC2	A	A	A	A
NPC3	A	A	B	A-
NPC4	A	B	C	B
NPC5	A	A	B	A-
NPC6	A	B	B	B+
UKN2 (cMINC)	A	B	A	A-
MESn	C	D	D	D+
UKN4 (NeuriTox)	A	A	A	A
NSR	C	D	D	D+
SYN	B	B	B	B
Nnff	B	A	B	B+
3Dh	B	C	C	C+

Bal-Price et al, 2018

Mapping of key biological targets for DNT → Identifying test methods for DNT targets → Evaluating assays readiness level → Testing chemical libraries and analysing data

- Identifying gaps and finding new assays
- Evaluating reproducibility of assays between labs
- Dev. of tiered-testing strategy
- Proposing a Guidance Doc.
- Encouraging case study applications under IATA case study project (Hazard Assessment Programme)
- Determining IVB performance (sens 82%, spec. 88%)

National initiatives for NAMs

EXTERNAL SCIENTIFIC REPORT

APPROVED: 2 May 2022

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Development of a Roadmap for Action on

New Approach Methodologies in Risk Assessment

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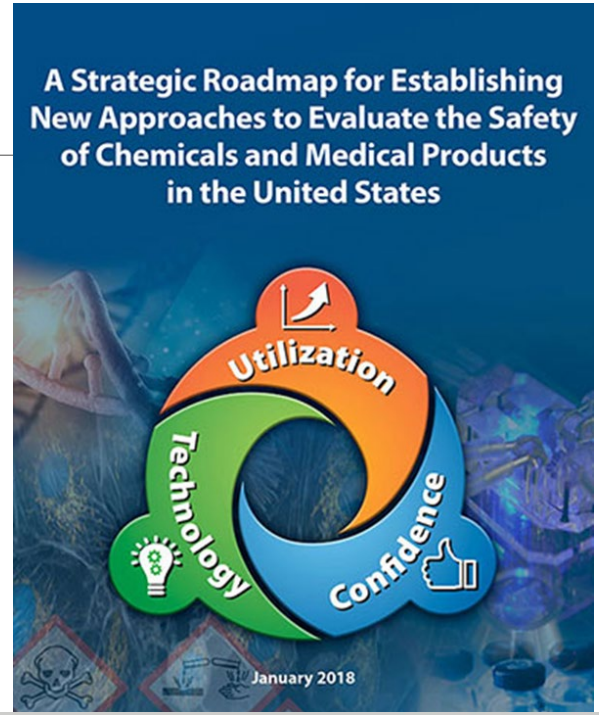
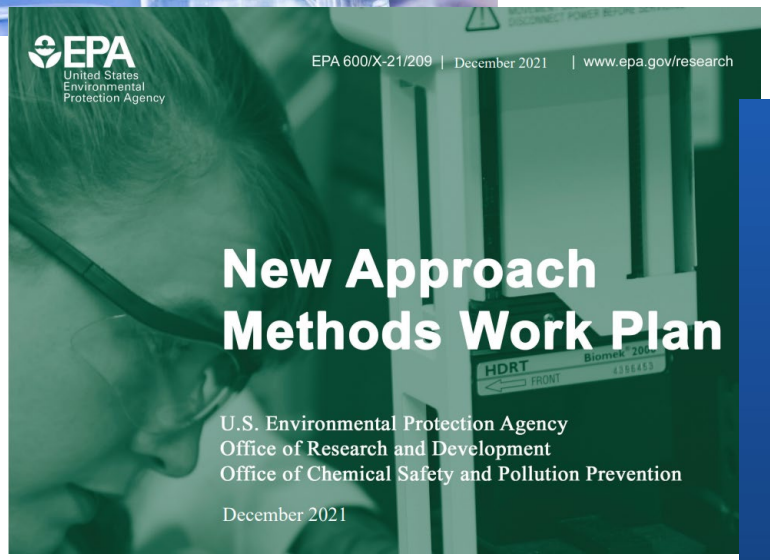
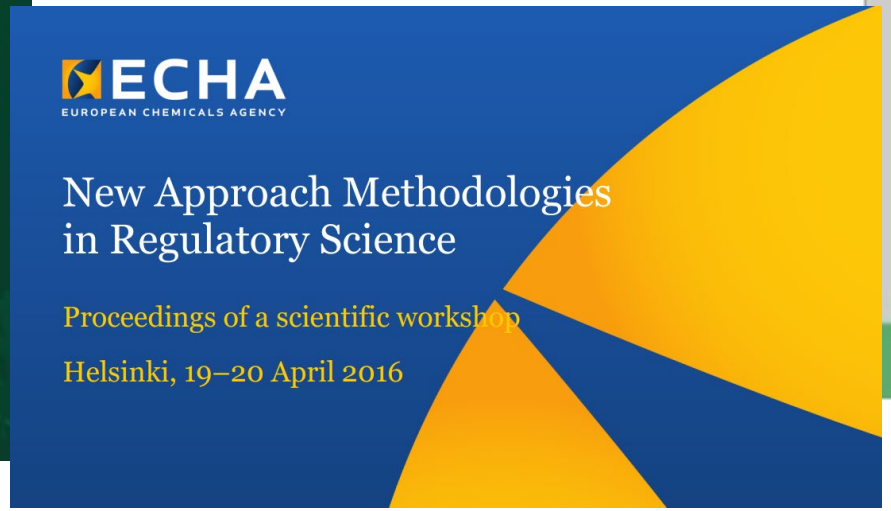






New approach methods for modern risk assessment

"OECD *supports use of **NAMs** when suitability can be demonstrated…*"

- **What counts as a "New Approach Method"?**
  - The OECD working assumption is **everything** that is **not an "old approach"**
    - *in chemico*, *in vitro*, computational, *in vivo* methods
    - stand-alone or (more often) integrated approaches to testing and assessment (IATAs)
    - data science/machine learning/AI (i.e. based on existing data)
  - Not "non-animal methods", but aligned with the 3Rs
    - Faster time to safety decisions
    - Less resources intensive

What is required for OECD adoption of NAM-based Test Guidelines

*"...when suitability can be demonstrated (to be **as good or better** than existing approaches)"*

- **What counts as "as good or better"?**
  - Results must be **reproducible**
  - The test system must be **relevant,** e.g.:
    - Sensitive to chemical-changes
    - Has a demonstrated relationship to the toxicological endpoint
    - Is **biologically relevant** to the target species
    - Should include a consideration of **approaches** that are **currently in use**
      - e.g. >80% do not have full suite of chemical safety data

The use of NAMs changes testing paradigms

- Regulations **vary** in:
  - Specific data requirements defined in regulations
  - Flexibility to fulfil requirements
  - Explicit national/organisational mandates to use NAMs
- **Creates potential divergence among countries & regulatory authorities**
  - A variety of NAM roadmaps
  - Use of NAMs is not harmonised
  - Potential threat to Mutual Acceptance of Data

OECD Integrated Approaches to Testing and Assessment (IATA) Case Studies Project

- Forum to share experiences with the use of novel non-standardised methods for chemical assessment in a regulatory context
  - Best practices and approaches
  - Identify aspects that can be harmonised
    - Standardised reporting formats
    - Structured data
- How to bring together new and existing information
  - How to use and **build confidence** in New Approach Methods (NAMs)
- **Not bound by MAD**, thus flexible, innovative approaches
  - Some of which **may become TGs**, e.g. TG 497 on Defined Approaches for Skin Sensitisation started as IATAs

How do you build confidence in NAMs?

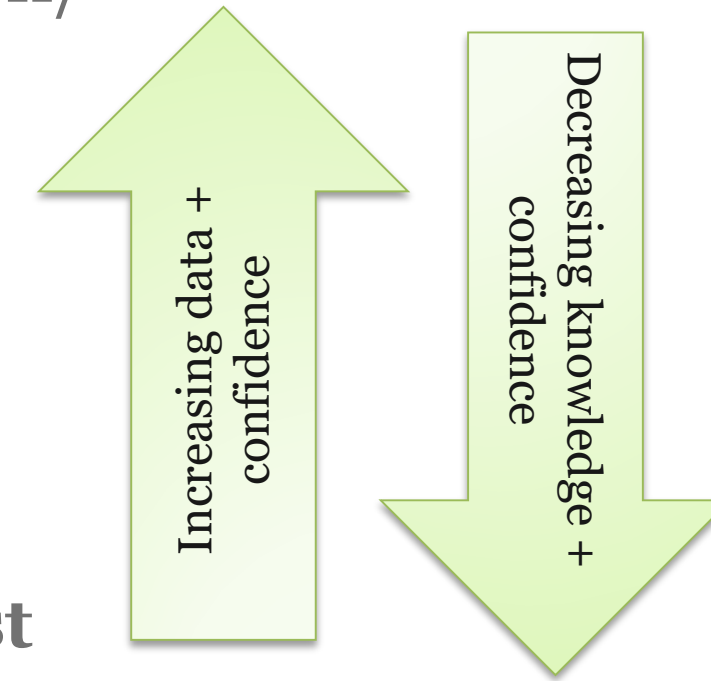
Documentation	• Clear problem formulation/context of use • Rationale for selection of method
Reproducibility	• Description/Standardisation of method • Demonstration of consistency over time/between users
Relevance	• Performance against robust set of reference chemicals • Consideration of relevance to target species (biology)
Uncertainty	• Transparent description of domain of applicability • Limitations (technical + lack of information)
Reviews	• Method and data documentation • Use of reporting standards for evaluation

Identify aspects that can be standardised

- Experience reviewing case studies has led to development/ refinement of a system of **reporting standards** that support:
  - Documentation
  - Initial problem formulation/ defining context of use
  - Peer review
  - Transparent reporting of
    - Technical limitations
    - Biological limitations
    - Limitations due to lack of information
  - Communication of the strengths/limitations of the approach

Internationally applicable solutions

- IATAs must have a clear regulatory application/ problem formulation; e.g.:
  - Risk assessment
  - Hazard characterisation (e.g. GHS)
  - Hazard identification
  - Prioritisation
- Suited to different types of chemicals, e.g.: cosmetics, agrochemicals, industrial chemicals
- **IATA acceptance does not mean countries must use the approach, <u>but they can chose to do so</u>**
- Likely to be a continuum
  - progress towards regulatory application that require more data/less uncertainty as more experience/knowledge is acquired



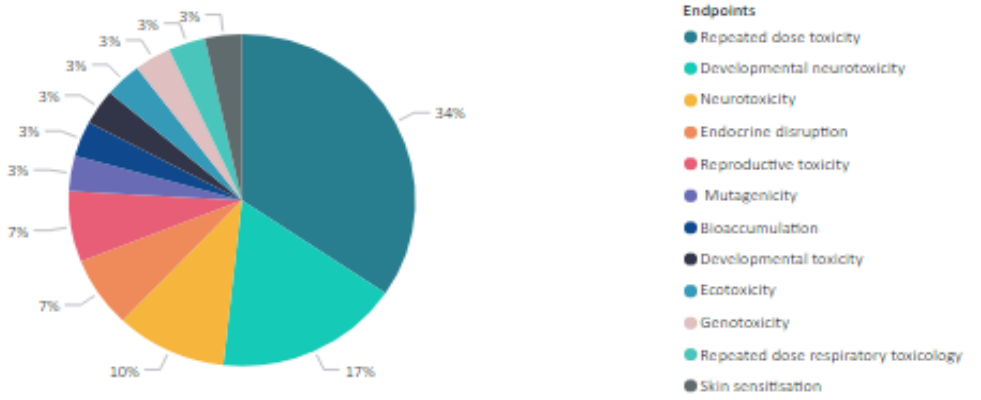
Case Studies on IATA

The OECD IATA Case Studies Project allows countries to share and explore the use of novel methodologies in IATA for chemical hazard characterisation within a regulatory context. In the interactive reports below, you will find:

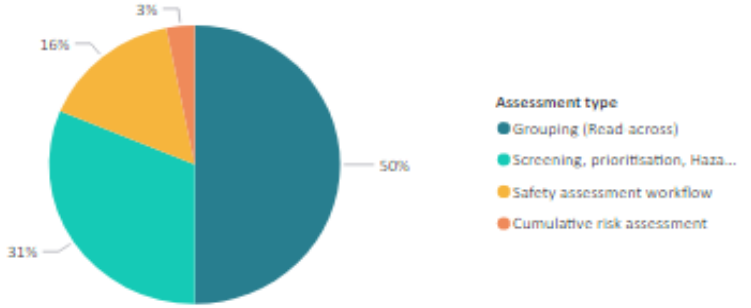
- The total number of case studies by endpoints, assessment type and IATA topics
- The full list and links to the case studies
- The consideration documents captures learnings and lessons from the review experience.

This report shows the number of case studies published by the OECD by **endpoints**, **assessment types** and **IATA topics**.

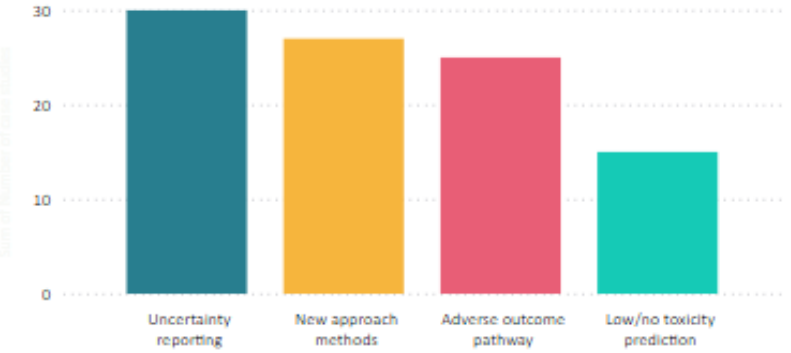
Number of case studies by endpoints



Number of case studies by assessment types



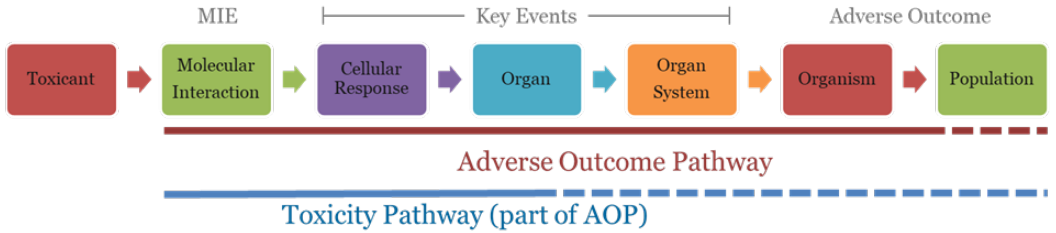
Number of case studies by IATA topics



[Series on Testing and Assessment: publications by number - OECD]

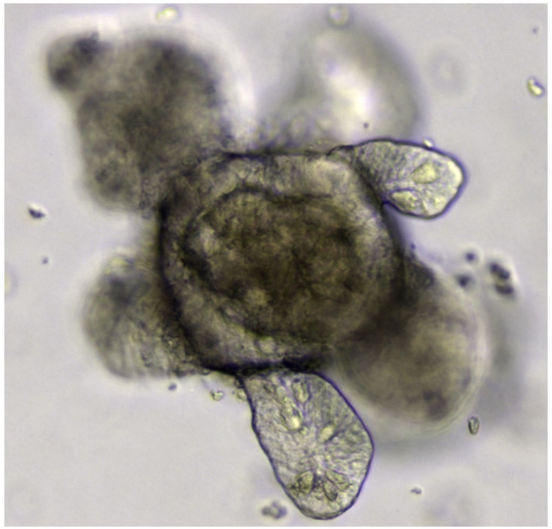
The first wave of NAMs: Mechanistic understanding and AOPs

- Pathway defined NAMs (i.e. AOP-amenable):
  - good understanding of mechanisms and key events
  - Establish plausible links between mechanistic and apical responses using existing test data and biological knowledge
  - approaches **predict** an **apical outcome**(s)



The next wave of NAMs: Physiological understanding

- Pathway undefined NAMs:
  - test systems that mimic [human] biology;
  - perturbation of signalling *could* lead to a variety of outcomes
  - changes are assumed to be undesirable
  - approaches **protective** against **potentially adverse effects**



By Meritxell Huch – http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002149, CC BY 4.0, https://commons.wikimedia.org/w/index.php?curid=40325751

*approaches not mutually exclusive

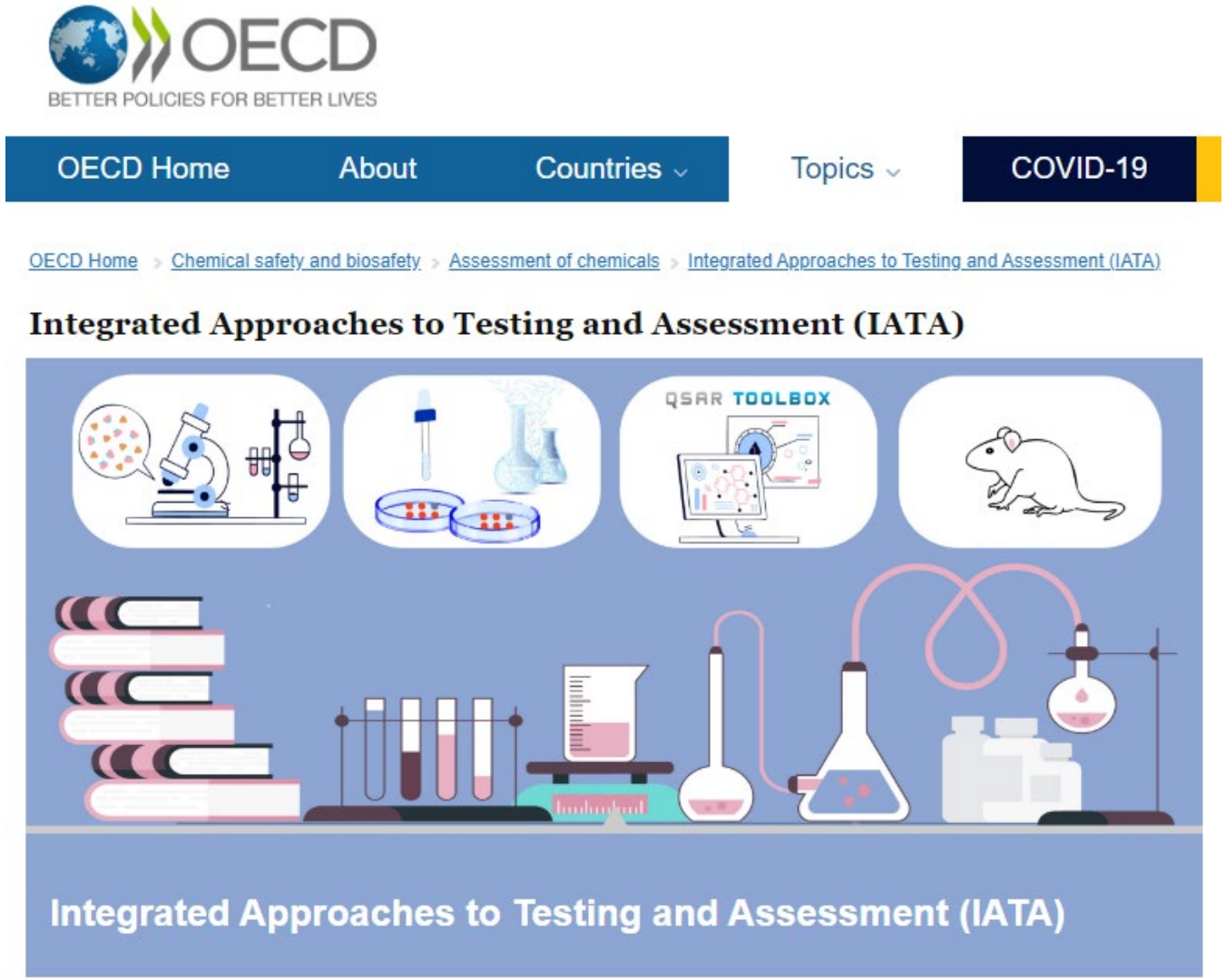
Evolution of IATA Case Study Project

- Increasing "usability" of case studies
  - Reduce resources requirements by "reusing" same IATA
  - Identify endpoints with regulatory data requirements that **do not have** NAM solutions
- Provide guidance for regulators via lessons learned in reviews
  - *Considerations* based on IATA Case Study Project reviews
  - Clusters of case studies addressing same endpoint
  - Identify knowledge gaps and priorities where additional guidance is needed
- Need more experience with IATAs addressing ecotoxicology endpoints
  - Most examples have focused on human health endpoints

What we need to get there

- Available data for review
  - Examples of hazard assessments comparing IATAs to traditional animal test data
- Continued engagement
  - IATA Case Study authors and reviewers
  - Communities of practice
  - Case Study authors and expert reviewers willing to contribute to guidance for use
- Engagement of regulators and data submitters to provide feedback
  - Retrospective engagement
    - NAMs that are submitted/reviewed
    - challenges/road blocks
    - possible solutions

Interested in learning more about IATAs? Visit the new interactive OECD IATA Website



Includes information on:

- What an IATA is and how they support chemical safety
- Resources and Guidance for authors on how to develop an IATA
  - Templates
  - Guidance
- >30 IATA Case Studies searchable by key words

Integrated Approaches to Testing and Assessment (IATA) - OECD

Recorded IATA Webinar

Find out more

Thank You For Listening

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