Integrated Approaches to Testing and Assessment: The Future of Regulatory Toxicology Assessment

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Conflict of Interest Statement

I declare I have no conflict of interest.

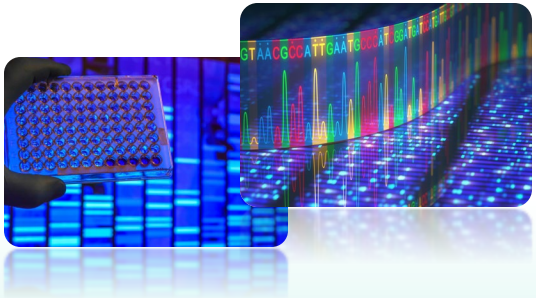
Overview

- Introduction
- What are IATA?
- Conceptual IATA workflow
- AOP and AOP-Informed IATA
- Types of IATA Elements
  - A Defined Approach to Testing and Assessment
- International Efforts
- Summary

Introduction

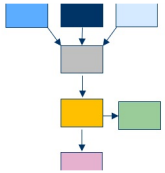
- Large no. of chemicals
- Traditional testing too resource intensive
- Limited mechanistic information

Integrated Approaches to Testing and Assessment (IATA)

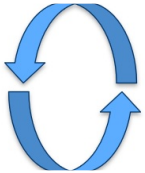


- New promising methods
- No stand-alone predictions

What are IATA?



- Structured approaches that integrate and weight different types of data for the purposes of performing hazard identification, hazard characterization, and/or safety assessment of a chemical or group of chemicals.



- An iterative hypothesis-driven approach to answer a defined question in a specific regulatory context, taking into account the acceptable level of uncertainty associated with the decision context.

- If the existing information is insufficient to address the safety decision under consideration, it guides the generation of new data, using both non-testing and experimental approaches, and AOP-based knowledge.

OECD (2016a), and Tollefsen et al., (2014)

Conceptual IATA Workflow

Existing data

AOP

Problem formulation
(Regulatory need, endpoint, constraints, acceptable uncertainty)

Hypothesis generation

Gather existing information
(Human data, *in vivo*, *in vitro*, non-testing data, phys-chem)

Hypothesis refinement

WoE

WoE assessment: Adequate information for decision-making?

Yes

Assessment conclusion

Generate new testing data

AOP

No

Generate additional information

Human data, (Q)SARs, *in vitro*, *in chemico*, High-throughput screening (HTS), *in vivo*, 3D-organoids, organs-on-chips, grouping & read-across, defined approaches

Chemical Exposure, ADME

No

Yes

Hypothesis refinement

WoE

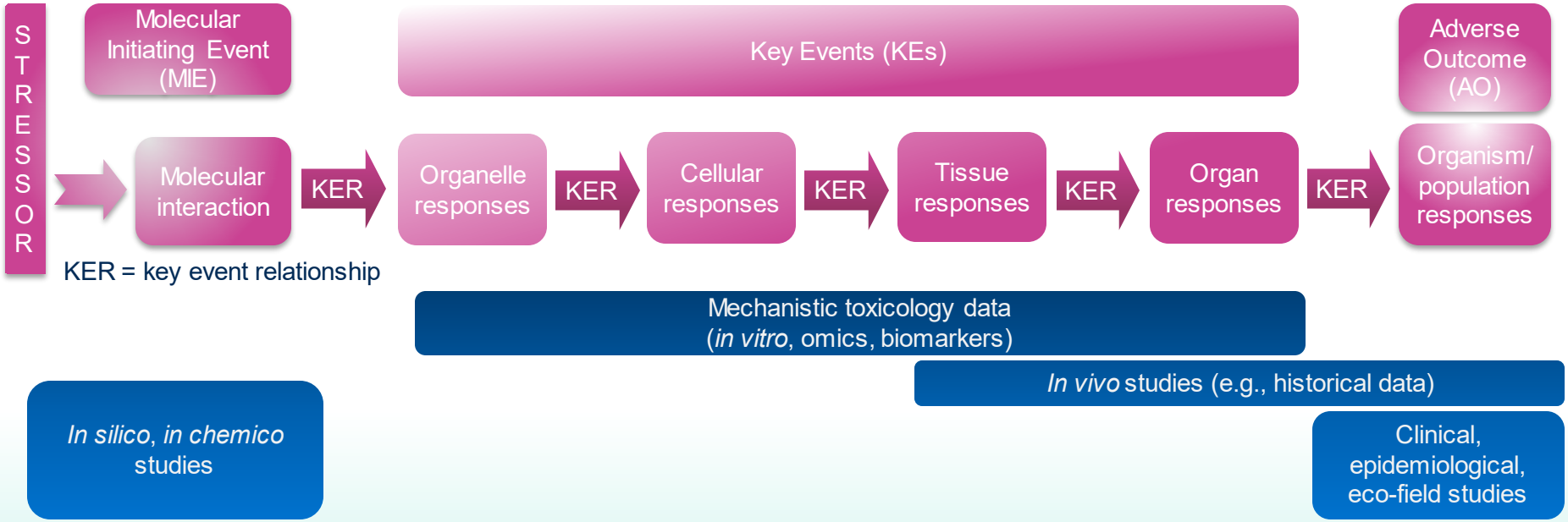
WoE assessment: Adequate information for decision-making?

WoE = weight of evidence

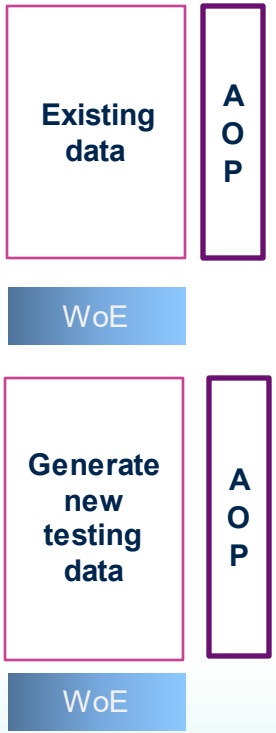
Figure re-adapted from OECD (2016a), and Bal-Price and Meek (2017)

Adverse Outcome Pathway (AOP)

- Simplified representation of toxicity pathways with key events (KEs) at various levels of biological organization
- Mapping, organization and integration of various types of information, around the MIE, Kes, and the AO



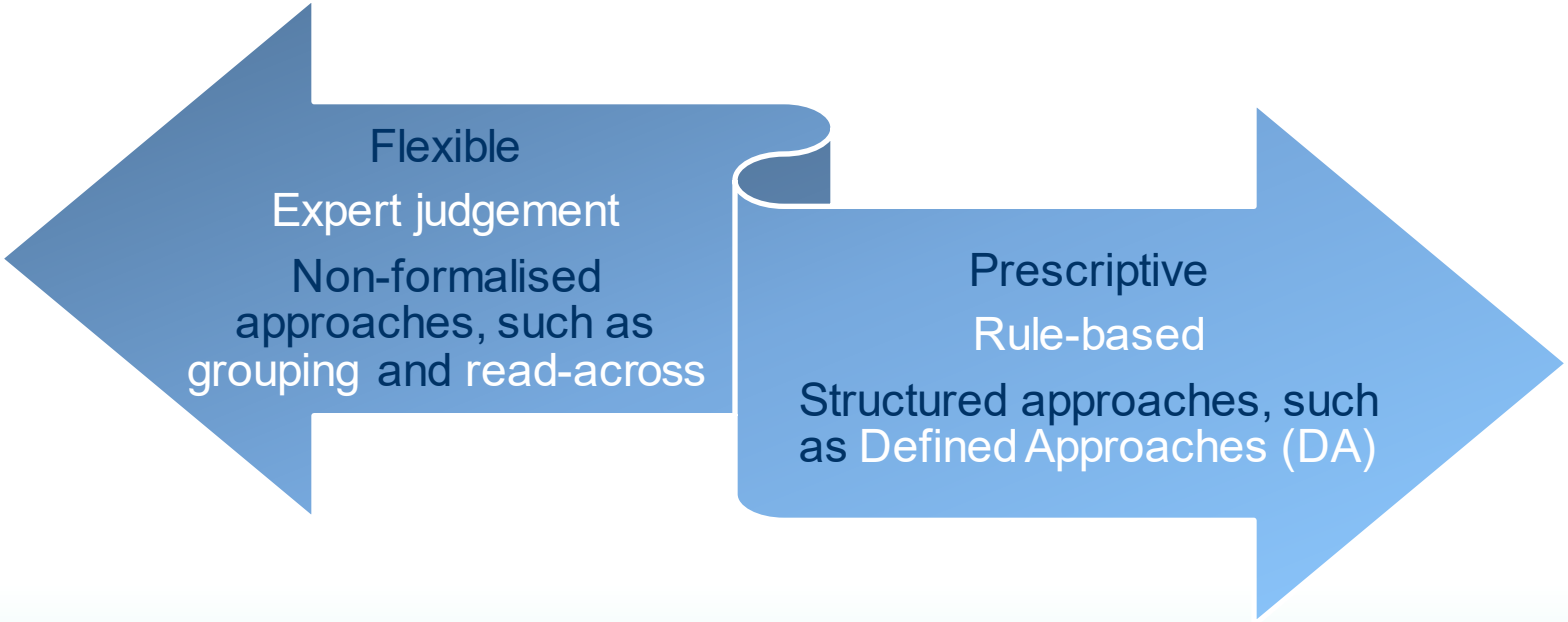
AOP-Informed IATA



- IATA should ideally be informed by mechanistic understanding
- The AOP framework allows to:
  - evaluate in a structured way the existing information for the chemical of interest
  - identify and generate the type of information and best test method per KE required to increase the level of confidence in the evidence, in an iterative way
- AOPs are expected to provide insight into the biological relevance, reliability, and uncertainties associated with the results from *in silico, in chemico, in vitro* and *in vivo* tests for regulatory use
- In determining the confidence for a given decision and the appropriate regulatory application, WoE for hypothesized AOPs should also be considered (*OECD AOP User Handbook*).

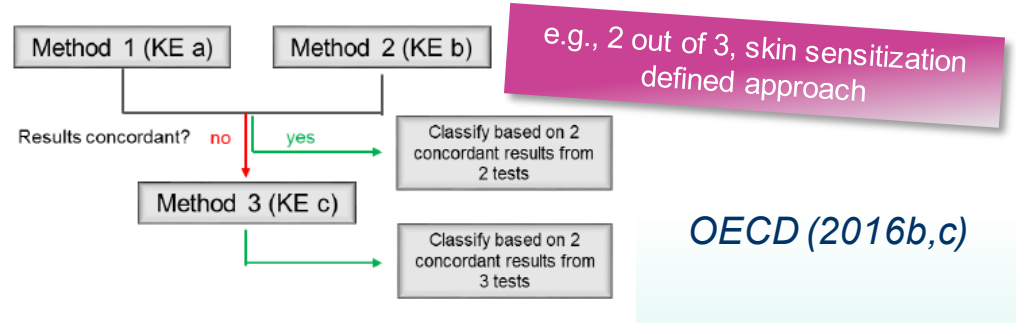
OECD (2016a, 2018a), and Tollefsen et al., (2014)

Types of IATA Elements



A Defined Approach to Testing and Assessment

- Fixed Data Interpretation Procedure (DIP) and defined set of information sources
- Fixed decision-making process, which provides regulatory consistency/certainty
- The final prediction can either be used on its own, or together with other information sources within an IATA, to satisfy a specific regulatory need



OECD (2016b,c)

- *Global Harmonization Efforts for Skin Sensitization IATA (Nicole Kleinstreuer)*

International Efforts (I)

- OECD IATA Case Studies Project
  - Launched in 2015 to increase experience with the use of IATA by developing case studies
  - So far, No. 23 case studies developed *(OECD, 2020)*
    - *Learnings and Recommendations from Four EU-ToxRisk Case Studies on Applying New Approach Methodologies Data to Support Read-Across (Susanne Hougaard Bennekou)*
    - *IATA as an Opportunity for Next-Generation Risk Assessment: The Propyl Paraben Case Study (Gladys Ouédraogo)*
- OECD GD on an IATA for Skin Irritation and Corrosion *(OECD, 2014)*
  - OECD TG 404 (Acute Dermal Irritation/Corrosion) updated
- OECD GD on an IATA for Serious Eye Damage and Eye Irritation *(OECD, 2018b)*
  - OECD TG 405 (Acute Eye Irritation/Corrosion) updated
- OECD GD on 12 Defined Approaches case studies for Skin Sensitization *(OECD, 2016c)*
  - Ongoing validation for the first 2 and easier Defined Approaches

International Efforts (II)

- U.S. EPA Defined Approach on Estrogen Receptor bioactivity *(Browne et al., 2015)*
  - Integration of high-throughput screening (HTS) assays into an ER Pathway computational model
  - Use of this defined approach has been accepted by the EPA as an alternative to three assays currently used in its Endocrine Disruptor Screening Program Tier I battery (*NTP, 2020*)

- NICEATM & U.S. EPA Defined Approach on Androgen Receptor activity *(Kleinstreuer et al., 2017)*
  - Integration of HTS data into an AR Pathway computational model
  - EPA is currently considering whether this approach is potentially useful for replacement of existing tests currently required in the Endocrine Disruptor Screening Program (*NTP, 2020*)

- Next Generation Risk Assessment (NGRA) Decision Framework for Cosmetics
  - *IATA as an Opportunity for Next-Generation Risk Assessment: The Propyl Paraben Case Study (Gladys Ouédraogo)*

Summary

- Tailored & predictive hypothesis-driven approaches which integrate existing knowledge on chemicals with mechanistic data across levels of biological organization (AOP), exposure, and other sources of information for targeted testing or assessment conclusions
  - Optimize resources
  - Go beyond hazard information, also including kinetics and exposure data
  - Increase confidence in the use and application of New Approach Methodologies (NAM) within safety assessment
  - Play a key role in shifting emphasis from traditional testing based on apical endpoints to hypothesis-based and mechanistic-driven testing strategies
- Defined approaches can facilitate the regulatory acceptance and use of IATA
- Prioritization, classification & labeling, hazard identification & characterization, and risk assessment

References

- Bal-Price A, Meek ME, 2017. Adverse outcome pathways: Application to enhance mechanistic understanding of neurotoxicity. Pharmacology & Therapeutics 179 (2017) 84–95.
- Browne P, Judson RS, Casey WM, Kleinstreuer NC, Thomas RS, 2015. Screening Chemicals for Estrogen Receptor Bioactivity Using a Computational Model. Environ Sci Technol. 2015 Jul 21;49(14):8804-14. doi: 10.1021/acs.est.5b02641.
- Kleinstreuer NC, Ceger P, Watt ED, Martin M, Houck K, Browne P, Thomas RS, Casey WM, Dix DJ, Allen A, Sakamuru S, Xia M, Huang R, Judson R. Development and Validation of a Computational Model for Androgen Receptor Activity. Chem. Res. Toxicol. 2017, 30, 4, 946-964.
- National Toxicology Program (NTP), 2020. Integrated Approaches to Testing and Assessment Webpage. Available at: https://ntp.niehs.nih.gov/whatwestudy/niceatm/integrated-testing-strategies/index.html (Accessed May 2020)
- OECD, 2014. New Guidance Document on an Integrated Approach on testing and Assessment (IATA) for Skin Corrosion and Irritation. Series on Testing and Assessment No. 203. ENV/JM/MONO(2014)19
- OECD, 2016a. Guidance Document for the Use of Adverse Outcome Pathways in Developing Integrated Approaches to Testing and Assessment (IATA). Series on Testing & Assessment No. 260. ENV/JM/MONO(2016)67.
- OECD, 2016b. Guidance Document on the Reporting of Defined Approaches to be used within Integrated Approaches to Testing and Assessment. Series on Testing & Assessment No. 255. ENV/JM/MONO(2016)28.
- OECD, 2016c. Annex I: Case studies to the Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be used within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitization. Series on Testing & Assessment, No. 256. ENV/JM/MONO(2016)29/ANN1.
- OECD, 2018a. User's Handbook Supplement to the Guidance Document for Developing and Assessing AOPs. Series on Testing & Assessment No. 233. Series on Adverse Outcome Pathways No. 1. ENV/JM/MONO(2016)12
- OECD, 2018b. Guidance document No. 263 on Integrated Approaches to Testing and Assessment (IATA) for Serious Eye Damage and Eye Irritation. Series on Testing and Assessment, No. 263. ENV/JM/MONO(2017)15/REV1.
- OECD, 2020. Integrated Approaches to Testing and Assessment (IATA) Webpage. Available at: http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm (Accessed May 2020)
- Tollefsen KE, Scholz S, Cronin MT, Edwards SW, de Knecht J, Crofton K, Garcia-Reyero N, Hartung T, Worth A, Patlewicz G, 2014. Applying Adverse Outcome Pathways (AOPs) to support Integrated Approaches to Testing and Assessment (IATA). Regulatory Toxicology and Pharmacology 70 (2014) 629–640.

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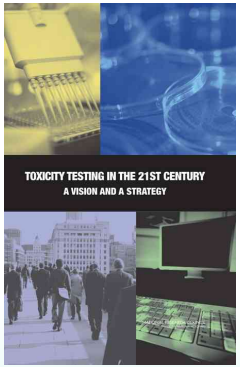
Thank you!

Back-up slides

New Approach Methodologies (NAM) in IATA

Overarching term for all methods and approaches not relying on animal testing



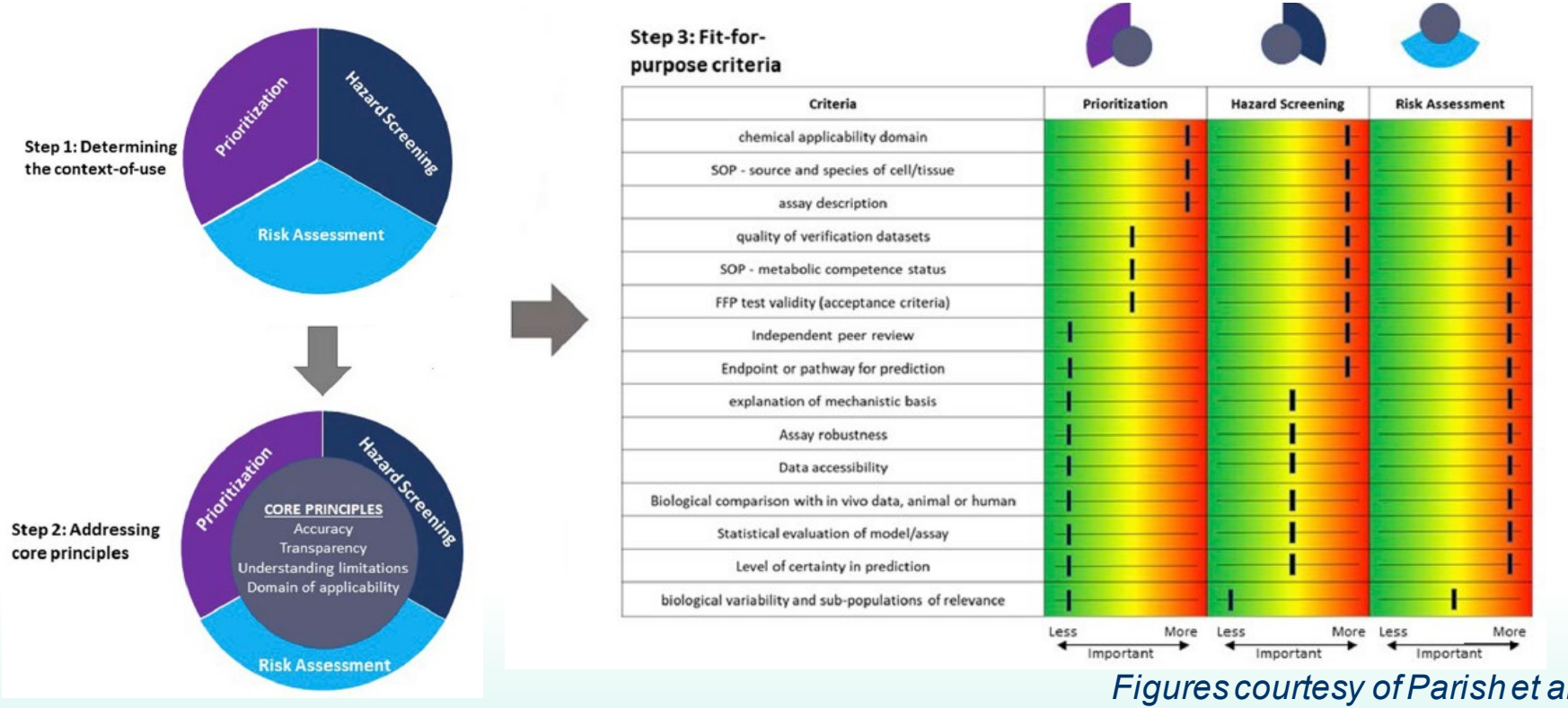
"Advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology could transform toxicity testing from a system based on whole-animal testing to one ***founded primarily on in vitro methods*** that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin"

"The mix of tests in the vision include tests that ***assess critical mechanistic endpoints*** involved in the ***induction of overt toxic effects rather than the effects themselves.***"

"The ***new toxicity-testing paradigm*** will be well suited to providing the relevant data needed to make the critical risk-management decisions required in the long term".

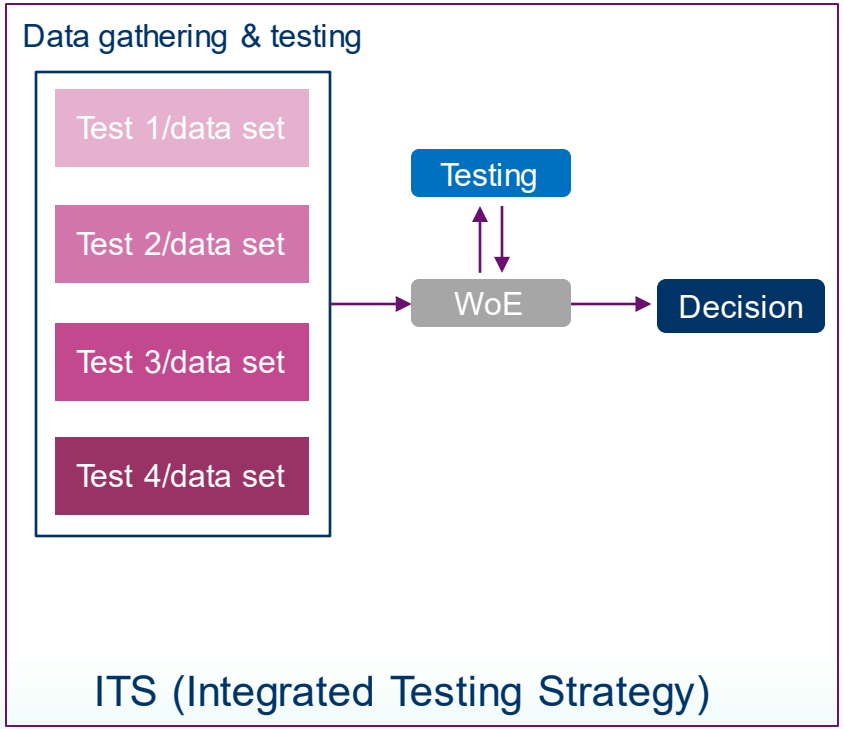
NRC, 2007

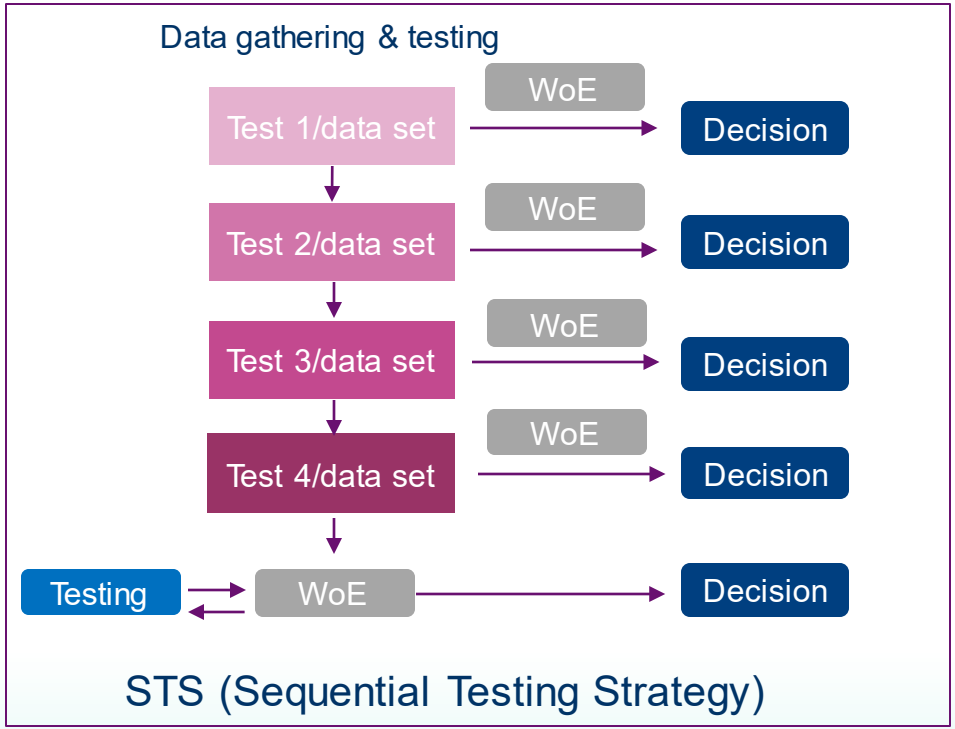
NAMs in IATA, and Fit-for-Purpose-Criteria



Figures courtesy of Parish et al., 2020

Possible Testing Strategies





(OECD, 2016b)