OECD PERSPECTIVE* ON BUILDING CONFIDENCE FOR NAMs

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OECD EHS/ENV
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BETTER POLICIES FOR BETTER LIVES

Mutual Acceptance of Data

The Gold Standards

Good Laboratory Practices

Harmonised Test Guidelines

OECD MAD Validation Standards

GLP Quality Assurance

- Criteria
  - Rigorous standards
  - Reporting and data storage requirements
  - Documented through a number of Guidance Documents
- Process
  - Certification
- Review
  - Inspected by National Authorities

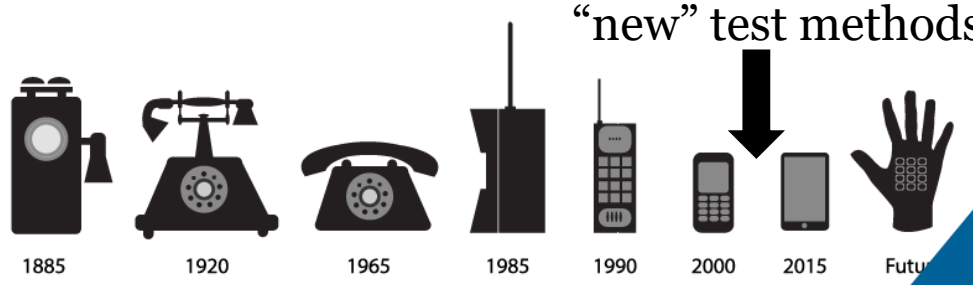
GL Scientific Validation

- Criteria
  - Principles outlined in GD 34
    - Reliable/relevant
    - Reproducible/transferable
    - Transparent
- Process
  - Intra-lab
  - Inter-lab
- Review
  - Experts (in/out of OECD)
  - National Coordinators
  - Written Comments

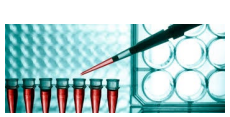
Advantages

Challenges

Nov	• SPSF submitted and reviewed by WNT, may be revised
Apr	• Approved projects are added to the TGP work plan
Sep	• 1st written commenting round (8 wks)
Nov	• Written response to consolidated comments; document revised
Dec	• 2nd written commenting round (6 wks)
Jan	• Written response to consolidated comments; document revised
Feb	• Final draft posted 6 wk before WNT meeting
Apr	• WNT approval
Jun	• Documents are pu



Skin sensitisation: Workflow for defined approach (1st NAM GL)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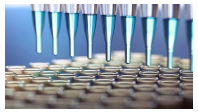
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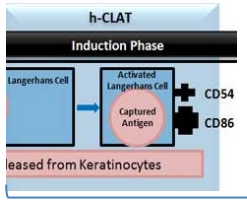
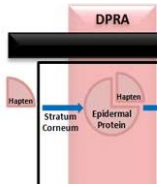
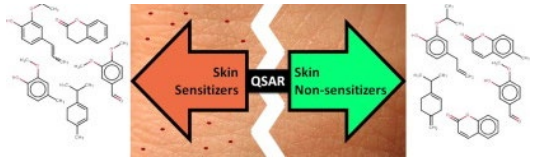






Defined information sources

Score	h-CLAT MIT	DPRA depletion	DEREK
3	≤10 µg/mL	≥42.47%	-
2	>10, ≤150 µg/mL	≥22.62, <42.47%	-
1	>150, ≤5000 µg/mL	≥6.376, <22.62%	Alert
0	not calculated	<6.376%	No alert

Potency: Total battery score		
	Strong :	6-7
	Weak :	2-5
	Not classified :	0-1

Defined data interpretation

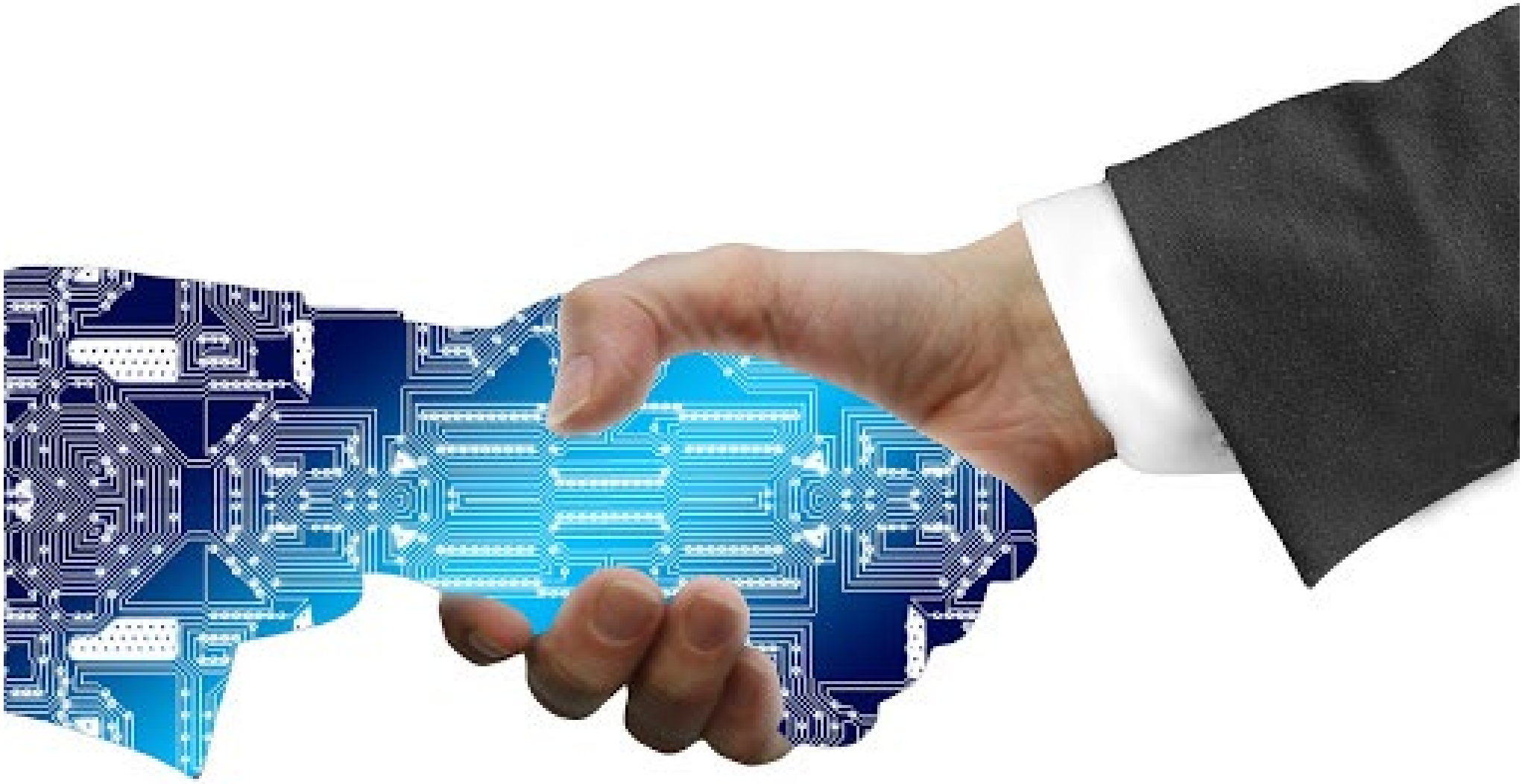
=

Methods A + B + C → **Predict the mouse!**

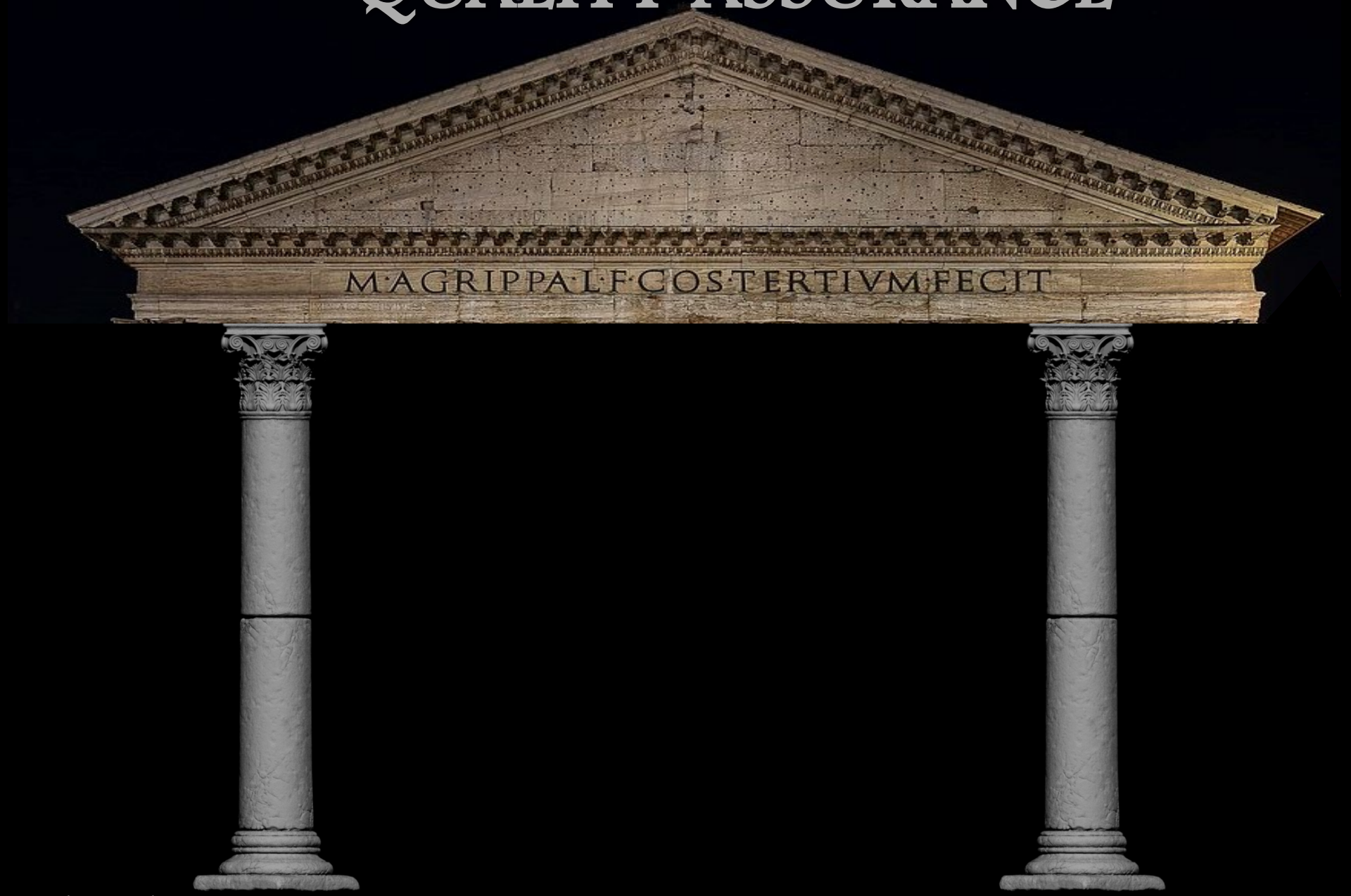
[OECD iLibrary | Guideline No. 497: Defined Approaches on Skin Sensitisation]

Mutual Acceptance of Data (MAD)

How to establish confidence in new approach methods



QUALITY ASSURANCE



Good Laboratory Practices

Good Computational Method Practices

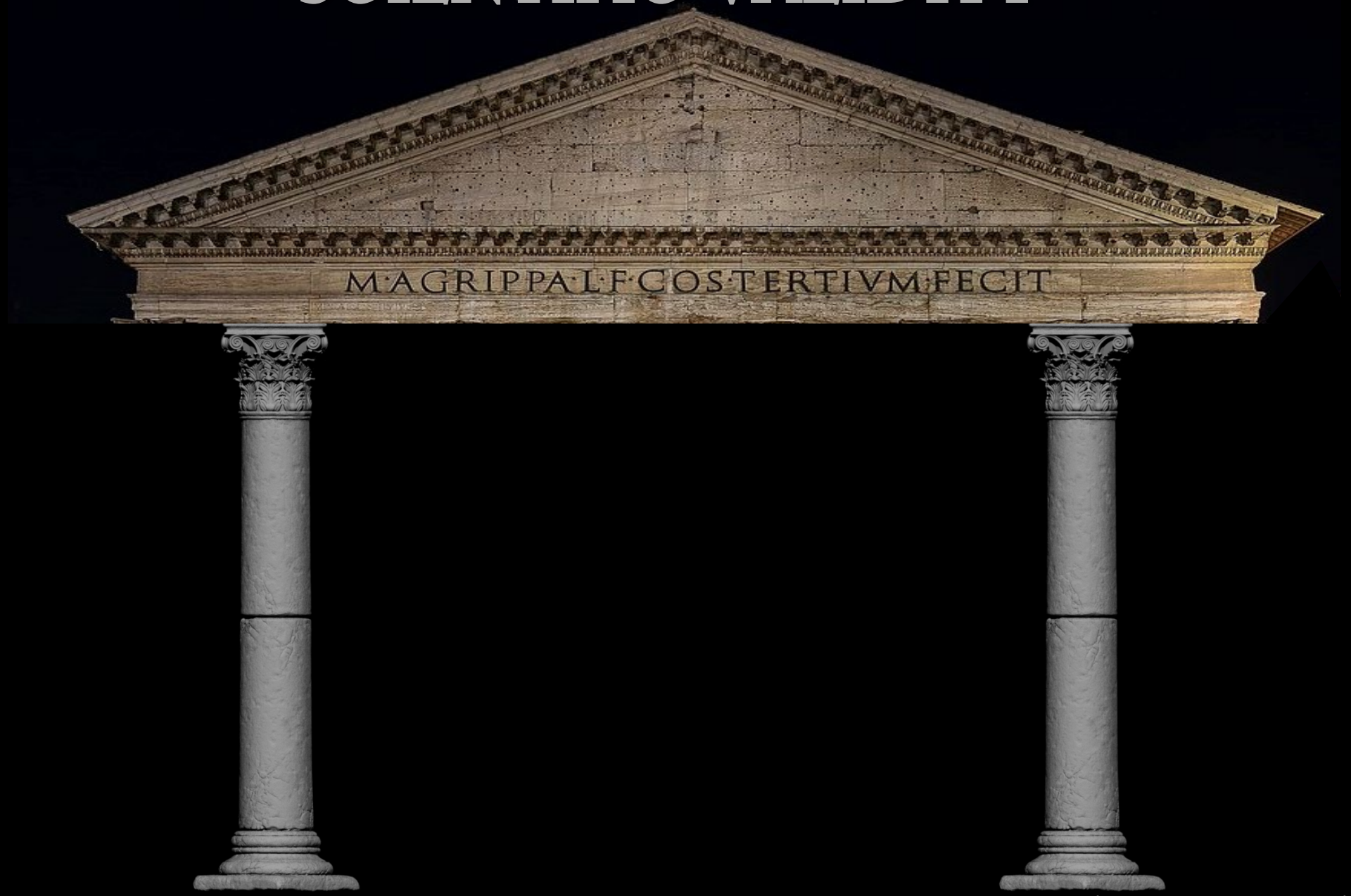
- OECD Concept of MAD can be expanded beyond traditional laboratory experimental data
  - Computational methods can be done in GLP environment and covered by MAD
  - But… they don't have to be
    - Some methods may not covered by MAD
    - But not **not** useful
  - Regulators have been accepting computational data for years
    - High confidence if:
      - Regulators can reproduce computational data on their own
      - Instructions for generating computational data are codified
- How can OECD facilitate the use of computational data/NAMs/other tools?

Table 1.	Quality Assurance Coverage ✓= QA guidance available; ✎ = drafting			
Potential single or combination of elements of existing or future OECD TG	Scenario 1 (all elements conducted in GLP laboratory)	Scenario 2 (in vitro or in vivo studies conducted in GLP lab and sponsor has the results; in silico prediction and DIP for combination of information sources carried out at study sponsor premises)		Scenario 3 (in vitro or in vivo studies conducted in GLP lab and regulator has the results; in silico prediction and/or DIP for combination of information sources carried out by regulator)
		A (Sponsor premises is part of GLP monitoring programme)	B (Sponsor premises is not part of GLP monitoring programme)	
In vivo model (in test facility)	✓ (GLP Guidance) ✓ (TG instructions)	Considered as multi-site study for GLP and otherwise Scenario 1 applies	✓ (GLP Guidance) ✓ (TG instructions)	Not a MAD scenario as company not submitting data to regulator; but regulator can follow TG instructions for conducting in silico prediction and/or DIP for combination of information sources
In vitro model (in test facility)	✓ (GLP Guidance) ✓ (TG instructions)		✓ (GLP Guidance) ✓ (TG instructions)	
In silico prediction model	✎ (GLP - generic guidance for emerging technologies) ✓ (TG instructions)		✓ (TG instructions) (conducted by sponsor)	
Data interpretation procedure applied to raw data of in vivo or in vitro model (in test facility)	✎ (GLP - generic guidance for emerging technologies) ✓ (GLP Guidance) ✓ (TG instructions)		✎ (GLP - generic guidance for emerging technologies) ✓ (GLP Guidance) ✓ (TG instructions)	
Data interpretation procedure used to combine outputs from various information sources (in vitro, in vivo and/or in silico)	✎ (GLP - generic guidance for emerging technologies) ✓ (TG instructions)		✓ (TG instructions) (conducted by sponsor)	
Documentation (result requirements and retention)	✓ (GLP Guidance) for retention ✓ (TG instructions) for what to document		Result document requirements in TG which would need to be submitted to regulator Retention of records not covered for non-lab components	
MAD applies	✓	✓	**In principle, MAD would not apply (because what would regulator be asking to be re-conducted?) But experts noted that based on the TG instructions, regulator would be able to reproduce in silico prediction and DIP on combination of information sources for QA purposes, and could therefore accept the results.**	In principle, MAD would not apply (because not about submission of results), but regulator could conduct parts of the TG themselves following the TG instructions

Standardized Templates and Reporting Formats

- IATAs
  - General template
  - Read across template
  - Guidance for building blocks in IATA
- Defined Approaches
  - to be used in IATA
  - New GL includes elements to stand-alone DA use
- QSARs
  - QSAR Model Reporting Formats
  - QSAR Prediction Reporting Formats
  - Expanding to be generalizable to in silico models
- Omics
  - Transcriptomics Reporting Framework
  - Metabolomics Reporting Framework
- OECD Harmonised Templates (OHTs) for chemical safety data
  - ~130 standard reporting formats for information used in risk assessment
  - GL and non-GL studies
  - Chemically agnostic
- AOPs
- Various guidance on how to use

SCIENTIFIC VALIDITY

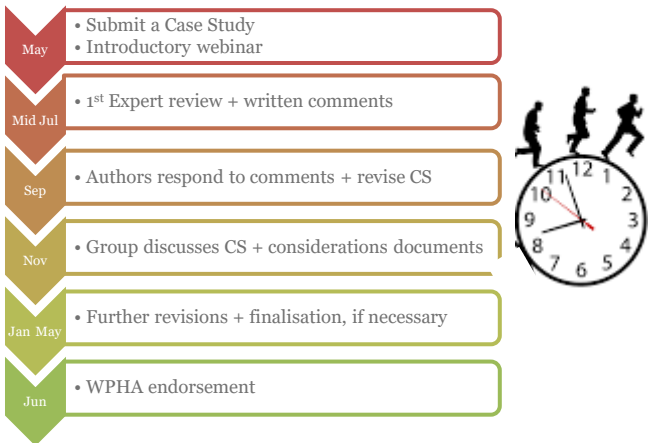


Harmonised Test Guidelines

OECD IATA Case Studies Project

Project of OECD Working Party on Hazard Assessment

- Increase experience with use of IATA by developing case studies providing examples that are fit for regulatory use
  - Exchange information on
    - Scientific approaches
    - Application in a specific regulatory context
    - Establish common/best practices
  - Create common understanding of using novel methodologies
    - Review/revise/publish case studies
    - generation of considerations/guidance on use of IATAs
  - Provide a possible path to
    - NAM use in TG
    - Defined Approach GL
    - Testing Strategies
    - Testing Batteries



- "Endorsement" by WPHA does not
  - indicate OECD Member Countries' agreement to use
  - bind countries in any decision making

- Results are not covered by the Mutual Acceptance of Data

Recent Publications Related to IATA CSP

- Guidance for using AOPs to build IATA/DAs

- Guidance for characterisation, evaluation and documenting of physiologically based kinetic (PBK) models (JRC/US lead) (March 2021)
  - OECD Nº 331
- Overview of Concepts and Available Guidance on Integrated Approaches to Testing and Assessment (IATA) and their Components (JRC lead) (Oct 2020)
  - OECD Nº 329

IATA Experience to date (+ 8 CS in this review cycle)

Year-No. (Lead)	Assessment Approach	Endpoint	IATA Topics AOP[1]	UR[2]	NAM[3]	L/N[4]	Reference
2020-1 (BIAC)	Safety assessment workflow	Repeated dose toxicity	X	X	X	X	OECD, 2021a
2019-1 (BIAC)	Safety assessment workflow Read-across	Reproductive toxicity	X	X	X	X	OECD, 2020a
2019-2 (BIAC)	Read-across	Repeated dose toxicity	X	X	X		OECD, 2020b
2019-3 (BIAC)	Read-across	Repeated dose toxicity	X	X			OECD, 2020c
2019-4 (BIAC)	Read-across	Repeated dose toxicity	X	X	X		OECD, 2020d
2019-5 (BIAC)	Read-across	Repeated dose toxicity	X	X	X	X	OECD, 2020e
2019-6 (BIAC)	Read-across	Developmental toxicity	X	X	X	X	OECD, 2020f
2019-7 (BIAC)	Read-across	Neurotoxicity	X	X	X		OECD, 2020g
2019-8 (BIAC)	Read-across	Neurotoxicity	X	X	X	X	OECD, 2020h
2018-1 (Japan)	Read-across	Reproductive toxicity	X	X			OECD, 2019b
2018-2 (US)	Prioritisation and screening	Oestrogenicity	X	X	X	X	OECD, 2019c
2017-1 (Canada/US)	Prioritisation and hazard characterisation	Oestrogenicity	X	X	X	X	OECD, 2018b
2017-2 (Canada)	Prioritisation of chemicals	Ecotoxicity	X	X	X	X	OECD, 2018c
2017-3 (JRC)	Read-across	Genotoxicity for nano-TiO_2		X	X		OECD, 2018d
2017-4 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2018e
2016-1 (Japan)	Read-across	Repeated dose toxicity		X	X		OECD, 2017b
2016-2 (US)	Grouping for cumulative risk assessment	Neurotoxicity	X		X		OECD, 2017c
2016-3 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2017d
2016-4 (ICAPO)	Read-across	Repeated dose toxicity		X	X	X	OECD, 2017e
2016-5 (JRC/BIAC)	Safety assessment workflow	Repeated dose toxicity	X		X		OECD, 2017f
2015-1 (Canada/US)	Read-across	Mutagenicity	X	X			OECD, 2016b
2015-2 (Canada)	Read-across	Repeated dose toxicity		X	X		OECD, 2016c
2015-3 (Japan)	Read-across	Repeated dose toxicity	X	X			OECD, 2016d
2015-4 (Japan)	Read-across	Bioaccumulation		X		X	OECD, 2016e

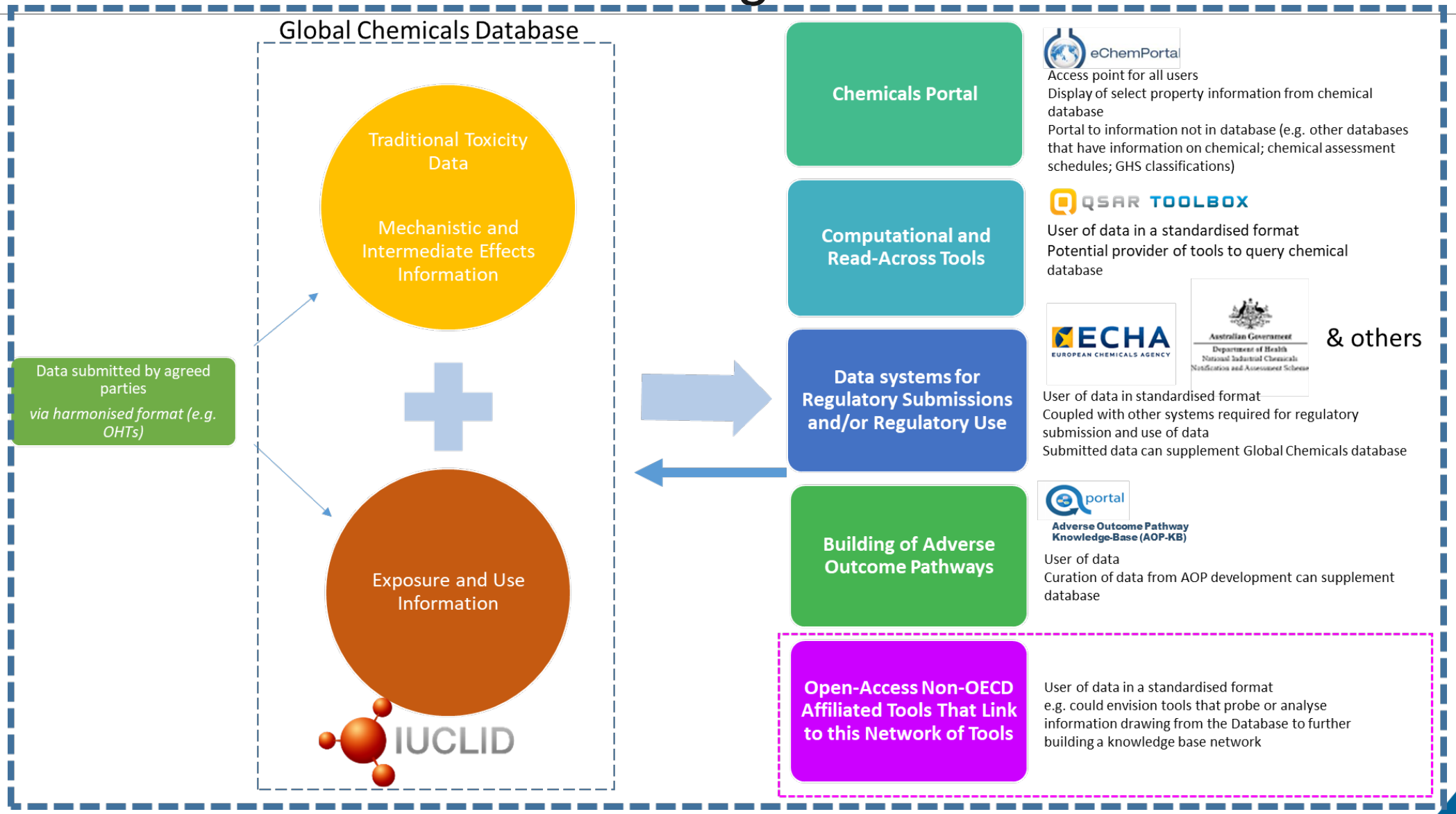
2014-2020

- 24 Cases studies have been published on OECD website

2021 = 7th cycle

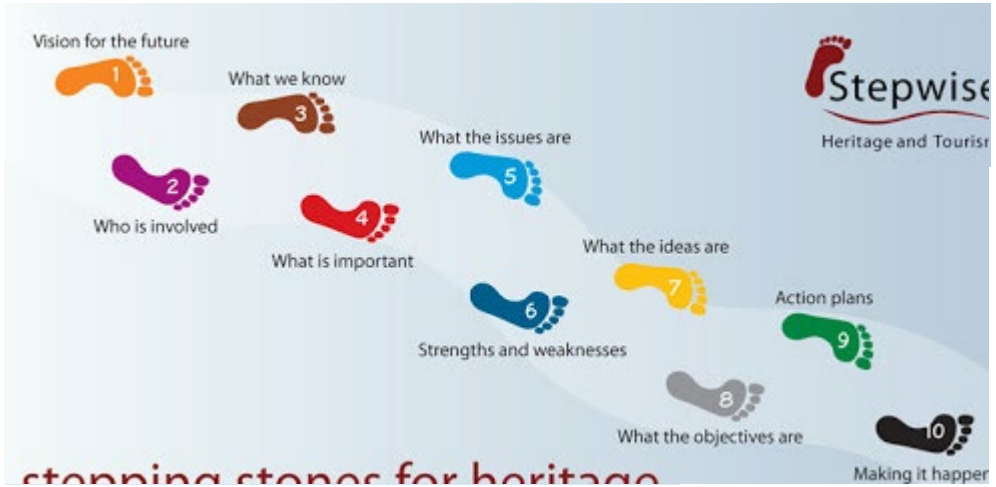
- 8 new case studies
  - 5 DNT
  - 1 NGRA Skin Sens
  - 1 inhalation toxicity
  - 1 transcriptomics for ED

OECD Electronic Ecosystem: Global Chemical Knowledge Base



21st Century technology in regulatory decision making

- **We're 21% through 21st century**
- How can we start using New Approach Methods for regulatory purposes in a step-wise fashion?
  - To gain experience
  - To build confidence
  - To help articulate what is needed at each step in the process



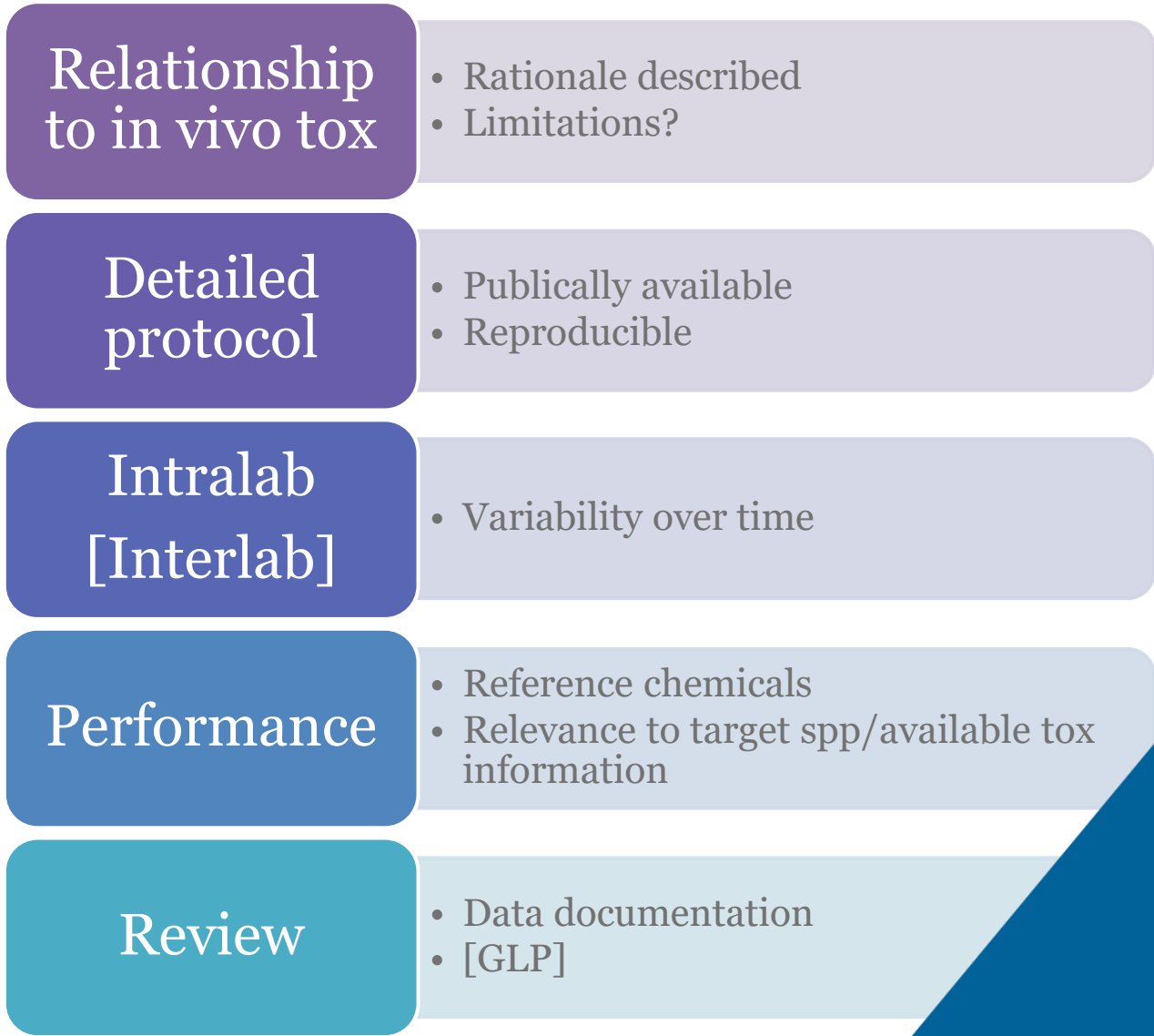
Consideration of how to demonstrate performance (reliability + relevance)

- Reference data
  - Do we need a system to predict the rodent to predict the human?
  - How many reference chemicals do we need?
    - Does this depend on the model system (e.g. human < rodent < in vitro < in silico)? If so, is that supported by logic?
    - Does this depend on how much we know about a toxicity endpoint (e.g. more for new pathways/endpoints that are less understood)? If so, is that an impossibly high bar?
    - Do reference chemicals need to be specific or can we make use (mechanistic) assays that may lead to a number of potential toxicities?

- Physiological validation
  - Can we establish indicators of what things a system SHOULD DO?
  - Can we use chemicals that are known to alter functions certain ways in certain systems?
  - Can we establish reference chemicals that are know organ-system specific toxicants?
  - Can we use these to establish confidence in methods for measuring chemical effects?

Tools to build confidence in NAMs

- Description of applicability domain/uncertainty
  - Due to lack of information
  - Due to limitation of methods
- SOP or standardised execution of the method
- Demonstration of reproducibility
- Predictive capacity of method(s) against robust reference chemicals
- Standardized reporting
- Agreed upon (or at least defined) vocabulary for method/effects/endpoints



Some parting thoughts

- We need
  - Practical perspectives on how to take up innovative approaches in a regulatory context
    - A harmonised test guideline is not the only solution
  - An AOP is not required to build an IATAs
- Governments spend 100M $/€ to support research on alternative methods, many of which do not become harmonised test guidelines
  - Need ways to use the available data and evaluate the suitability and confidence for uptake in a regulatory context
- Rather than asking if these are “ready for regulatory use”, maybe we should be asking **what is missing from the “confidence checklist”**?
  - Use the same vocabulary and terms considered for “traditional” test methods