OECD WORK ON INTERNATIONAL ACCEPTANCE OF NAMS

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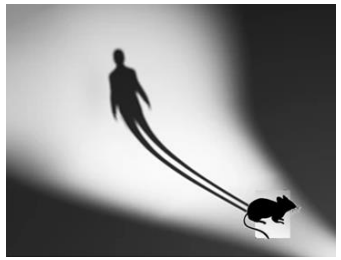
BETTER POLICIES FOR BETTER LIVES

Drivers for increase uptake of NAMs

- **Throughput**
  - Testing requirements vary may include a number of (sequential) experiments = months to years to produce and analyse data
  - Using traditional (mostly animal-based) methods for assessing safety, only 10s/100s/1000s of chemicals can be evaluated each year
- **Costs**
  - Bringing new products to market estimated:
    - Average for new drugs 1.3B USD
    - New pesticide active ingredients 250M USD
    - Cosmetics R&D in Europe 2.35B Euro/yr



- **Timeliness of decisions**
  - More rapid decisions may have human/environmental health benefit even with higher uncertainty
- **Relevance**
  - There is increasing recognition that the animal tests may not be good predictors of effects in humans
- **Changing regulations** which **reduce or prohibit animal testing** to evaluate chemical safety

OECD Test Guidelines & NAMs

- OECD Test Guidelines include that NAMs (not exhaustive)

Acute Toxicity	OECD publications
Oral	GD 237 ; TG 420, 423, 425
Dermal	GD 237; TG 402
Inhalation	GD 237, GD 39; TG 403, 433, 436
Eye Irritation and damage	GD 263; TG 437, 438, 460, 491, 492, TG 467
Skin Irritation and corrosion	GD 203; TG 430, 431, 435, 439, 460
Skin sensitisation	GD 256; TG 442C, 442D, 442E, TG 497

General Guidance	OECD publications
Grouping chemicals /read across	GD 194
Waving or bridging (read-across) acute toxicity tests	GD 237
Use of AOPs for Developing IATA	GD 260
Reporting DA to be used within IATA	GD 255
Describing non-guideline in vitro test methods	GD 211
Workshop report on framework for development and use of IATA	GD 215

- Results of OECD TG covered by **MAD**
- TGs describe methods for **generating data to evaluate hazard independent of regulatory framework**
  - Include some interpretation of hazard (Y/N, quantitative data)
  - Do not (generally) include outputs for specific frameworks (e.g. GHS)

The use of NAMs may challenge MAD

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

- MAD regards information sharing among Member Countries that have **the same data requirement**
  - **Divergence in acceptability may jeopardise MAD**

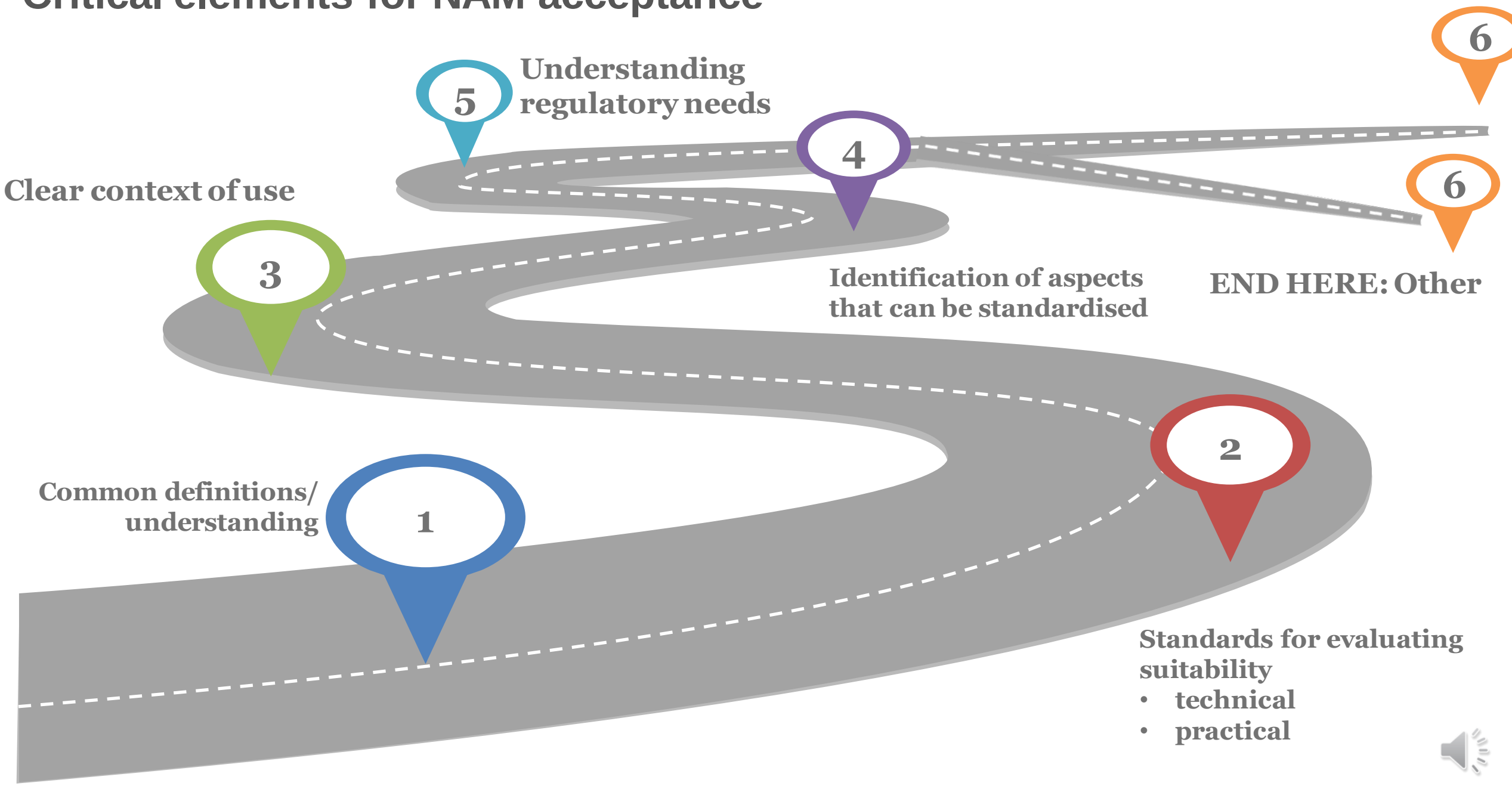
OECD Hazard Assessment & NAMs

Best approaches and practices for **integrating information to come to a regulatory decision on chemical hazard**

- Discussion of use of NAMs in a regulatory context
  - IATA Case Studies
  - Chemical grouping
  - QSAR Toolbox + other electronic tools
  - Omics approaches
  - Various topic-specific guidance documents
- Forum to discuss how to **build confidence in NAMs**
  - **identification of aspects that can be harmonised**

- **Not bound by MAD**
  - thus flexible, innovate approaches, some of which **may become TGs**

Critical elements for NAM acceptance



Common understanding

- **What is an OECD "new approach method"?**
  - "**New Approach Methods**" include **everything that is not an "old approach"**
    - *in chemico*, *in vitro*, data science, computational, *in vivo* methods
    - stand-alone or (more often) integrated approaches to testing and assessment (IATAs)
  - Not "non-animal methods", but aligned with the 3Rs
    - Faster time to safety decisions
    - Less resources intensive
      - e.g. cheaper, less time for testing/analyses, fewer/no animals used

Standards for evaluating suitability

- **What counts as "as good or better"?**
  - Results must be **reproducible**
    - Using a method that is scientifically robust
    - Documented in sufficient detail
    - Following the same approach, results can be repeated
  - The test system must be **relevant**
    - "**Relevance**" may vary with a specific **regulatory application**; e.g.
      - Sensitive to chemical-changes
      - Has a demonstrated relationship to the toxicological endpoint
      - Is biologically relevant to the target species

Standards for evaluating suitability

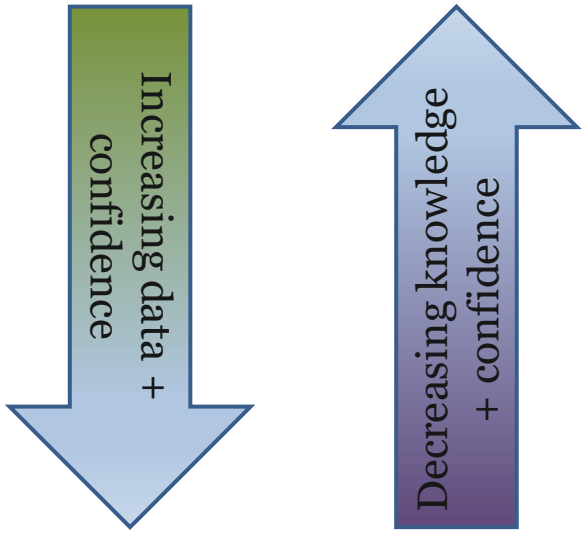
- Should include a consideration of **approaches** that are **currently in use**
  - Some NAMs perform as well/better than the in vivo reference test method
  - >70% do not have full suite of chemical safety data

Sufficient data for chemical assessment

Limited or no data

Clear context of use

- Need examples of NAM solutions for a variety of regulatory contexts
  - data rich/data poor chemicals
  - across chemical sectors/regulations
  - various regulatory problem formulations
    - Prioritisation
    - Hazard identification
    - Hazard characterisation
    - POD
    - Risk assessment



- Likely to be a continuum
  - more data/less uncertainty as more experience/knowledge is acquired

Identification of aspects that can be standardised

Reporting

- QSARs: QMRF/QPRF
- MIE/KE/KER
- Omics: OORF
- Test data: OHTs
- PBK
- Grouping/Read-Across
- Components of IAs

Guidance on use

Integration/Evaluation

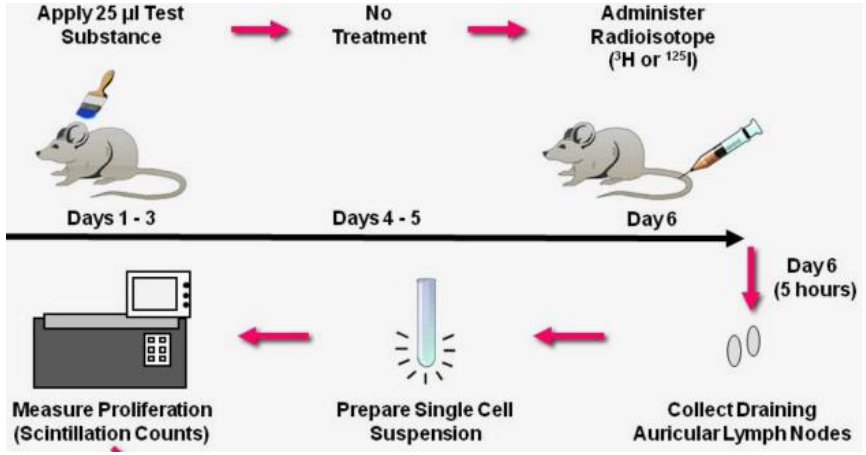
- AOPs
- QSAR Assessment Framework
- OECD IATA case studies
  - General examples
  - Endpoint-specific
  - Framework-specific

- Standardisation facilitates review and uptake of NAMs
  - Allows regulators to
    - become familiar with elements of the method
    - rapidly assess adequacy of information
    - easily share information
    - easily link information to existing chemical databases

Understanding the regulatory needs

Q: What information do regulators need to assess chemicals?

A: Typically, not the raw data resulting for experiments.



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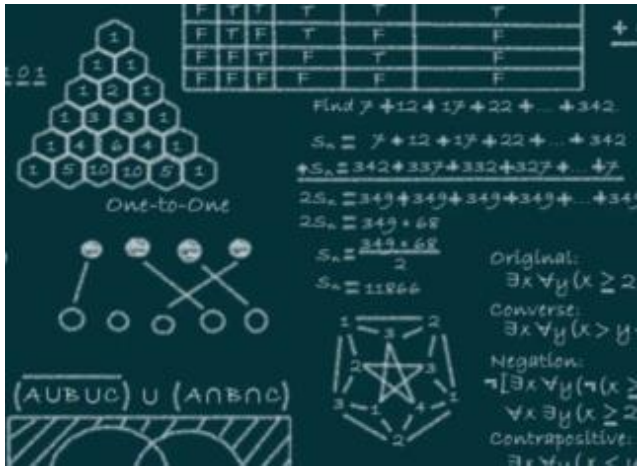

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Understanding the regulatory needs

The right NAM for the job: integrating information sources to overcome limitations of stand-alone methods, address relevant biology, and meet regulator needs

Step 1:

NAM TGs based on what was available

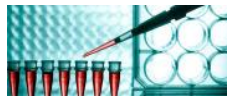
Step 2:

develop NAMs with intended purpose

Step 3:

build NAM batteries to address biology

Understanding the regulatory needs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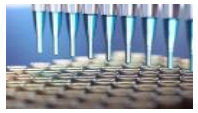
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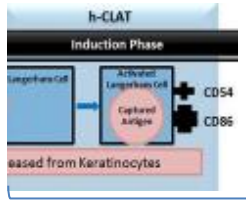
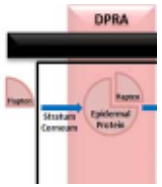




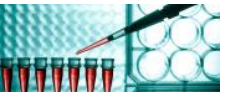
Defined information sources

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

Hazard Classification
(GHS potency subcategories)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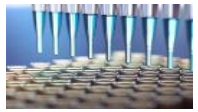
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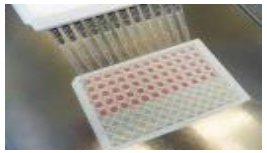
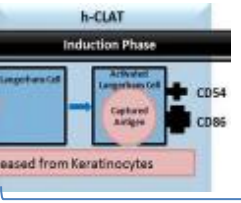
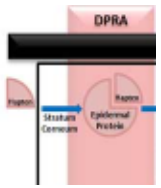
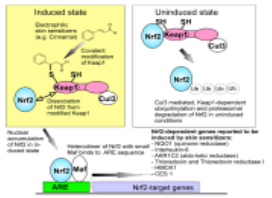
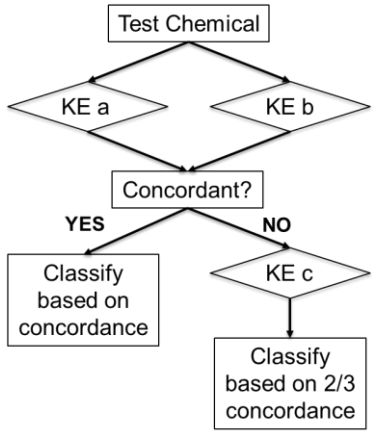








Defined information sources

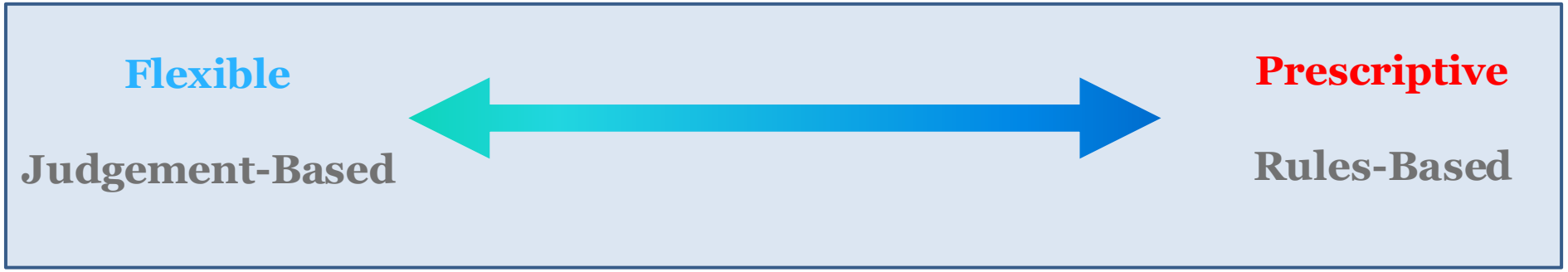


Defined data interpretation

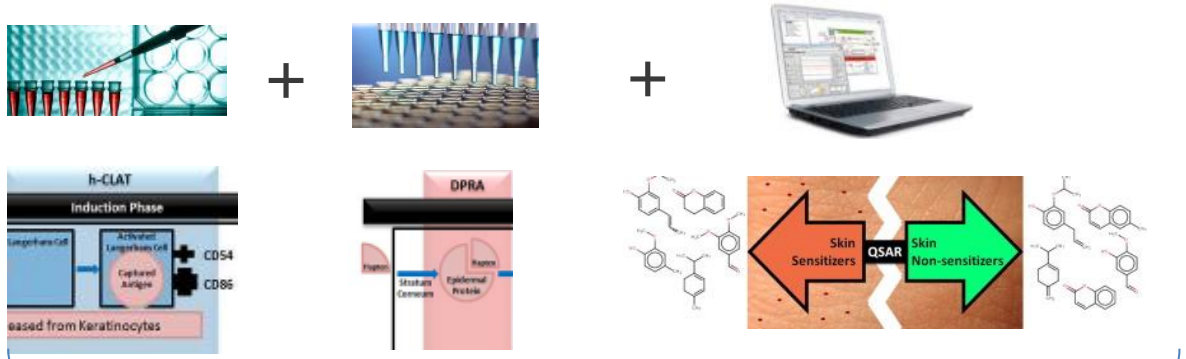
Hazard Identification
(sensitiser/non-sensitiser)

Putting it all together

IATA	Defined Approaches
Designed in response to problem formulation	Designed to address pre-defined endpoint/prediction
Inputs are defined by user	Defined information sources
Sequence of input, next steps, decision context defined by user	Sequence defined and next steps are rule-based
Expert judgement for weighting data, interpreting data	Fixed data interpretation procedure
Conclusion may be open to interpretation	Regulatory conclusion is clear



END HERE: Test Guideline Defined Approach Skin sensitisation



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Defined data interpretation

Methods A + B + C

Predict the mouse!

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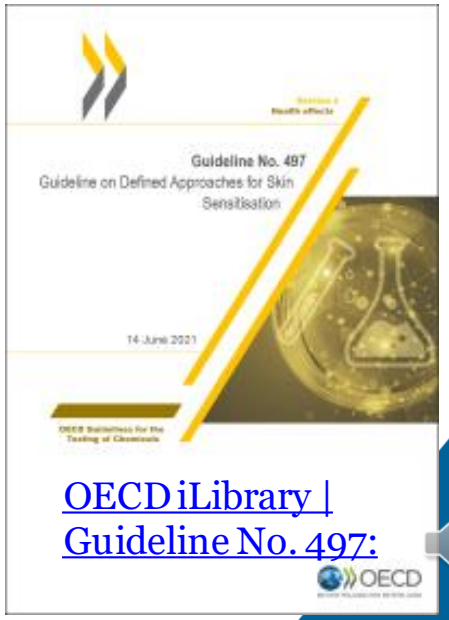
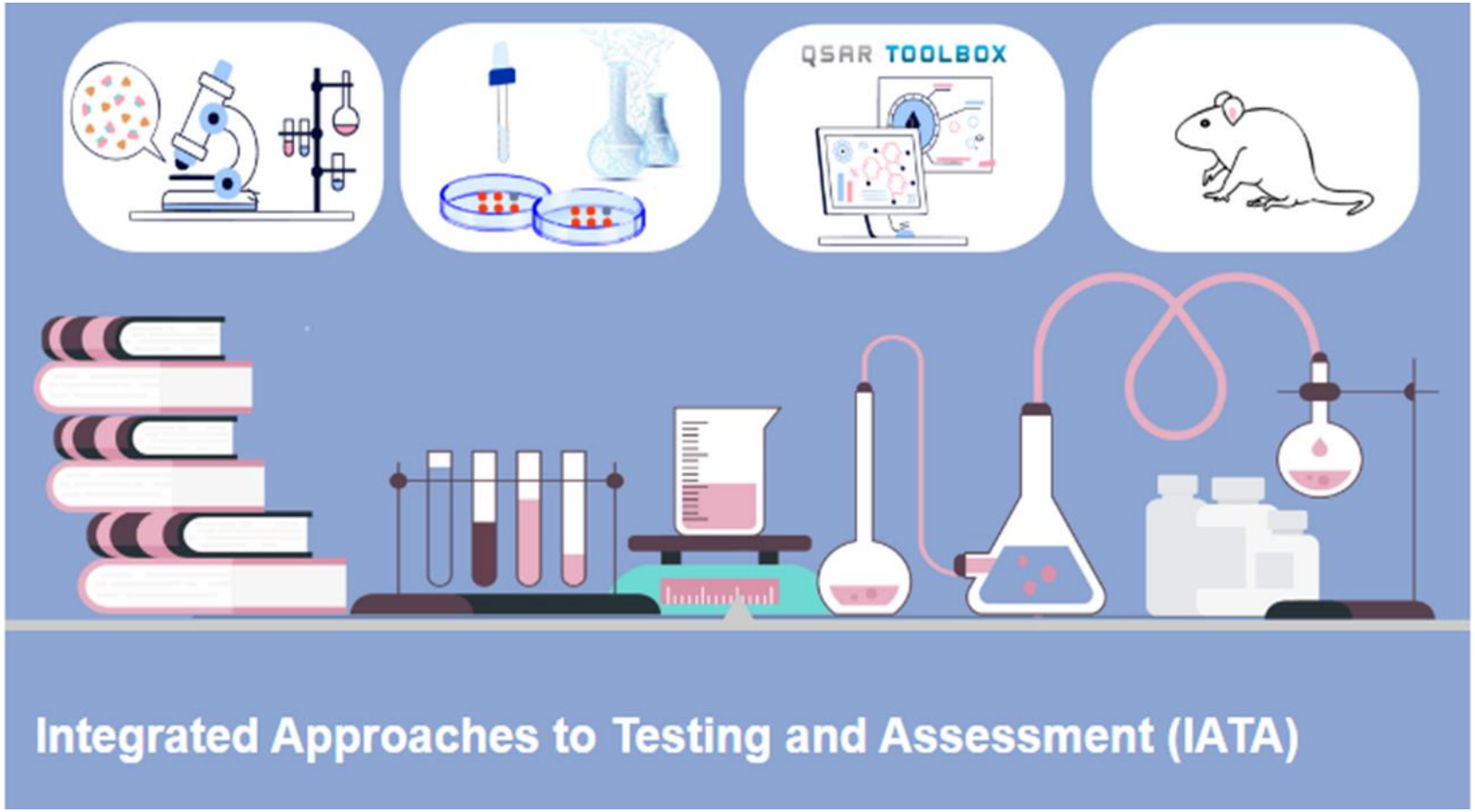


OECD iLibrary | Guideline No. 497:

END HERE: Other Integrated Approaches to Testing and Assessment



Why it is unique

- Examples used in a regulatory context
- Drafted by data submitters or regulators
- Document:
  - information sources,
  - approach for data integration
  - expert judgements
  - uncertainties
  - conclusions
- Often compared to “traditional” approach for assessing endpoints
- Independent peer reviewed by regulators
  - includes questions regarding global applicability
- Leads to guidance for NAMs
- Provides path for:
  - “opt-in” use w/out modification
  - Future TGs

END HERE: OTHER
Approaches or aspects that can be used

- Rather than asking if NAMs are “ready for regulatory use” can consider
  - **How can these methods be used now?**
  - **What is missing from the technical considerations?**
  - **What is missing from the implementation considerations?**
  - **How do we separate the results/read out from NAMs and the fit into regulatory decisions?**

Find out more

Thank You For Listening

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