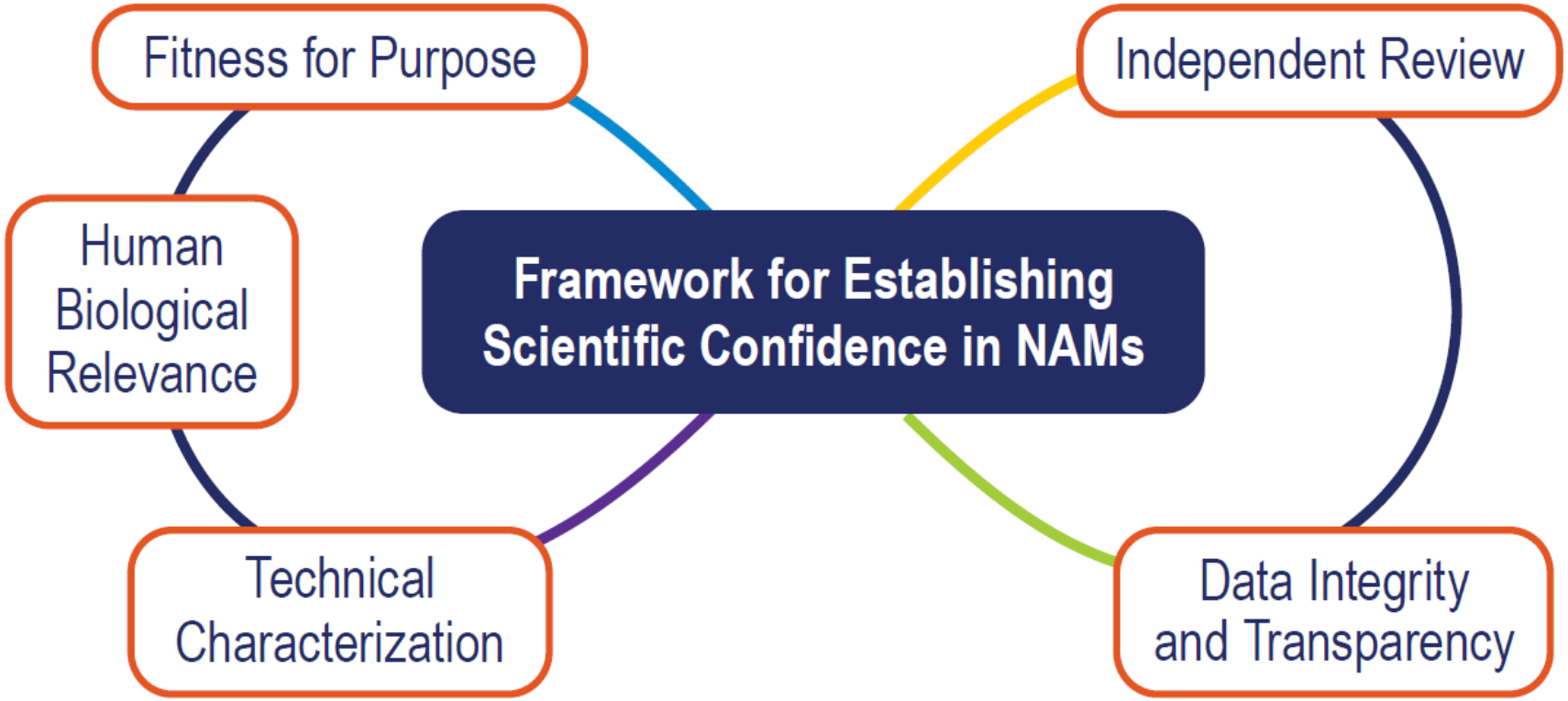
Establishing scientific confidence in New Approach Methodologies (NAMs)

Transparency, data integrity, external review and ring trials

João Barroso (Joint Research Centre, EURL ECVAM)

SACATM meeting, 22 September 2022

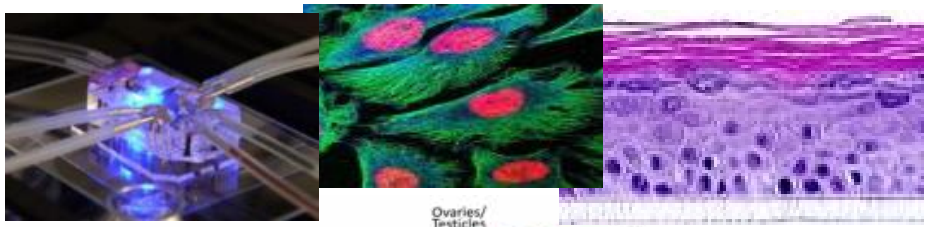
A framework for establishing scientific confidence in new approach methodologies



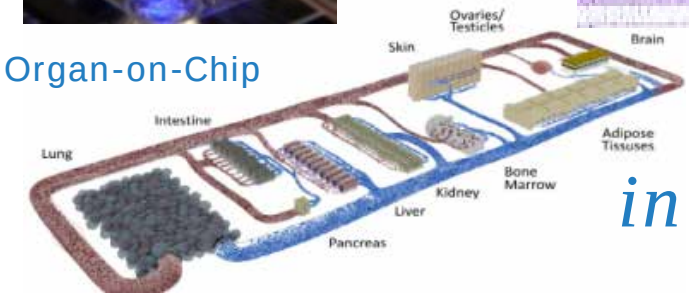
van der Zalm AJ, Barroso J, Browne P, Casey W, Gordon J, Henry TR, Kleinstreuer NC, Lowit AB, Perron M, Clippinger AJ. Arch Toxicol. 2022. doi: 10.1007/s00204-022-03365-4

https://link.springer.com/content/pdf/10.1007/s00204-022-03365-4.pdf

The modern safety assessment toolbox

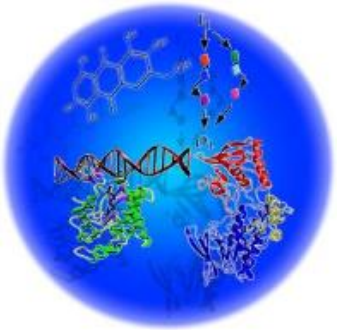


Organ-on-Chip



in vitro

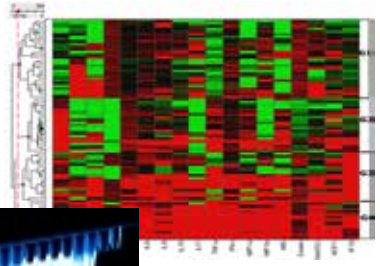
in silico

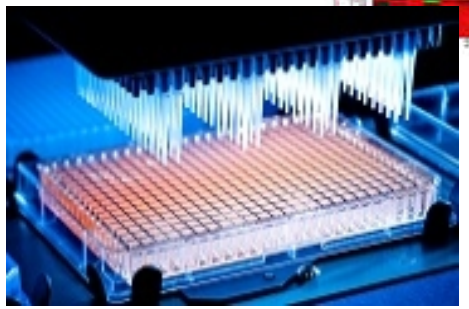


clinical data

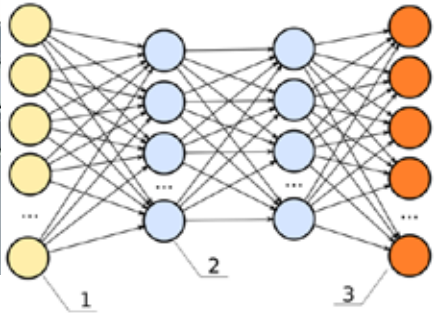
existing animal data

'omics

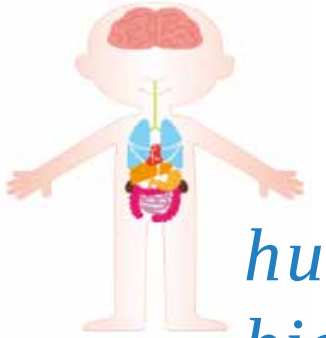




machine learning/AI



biokinetics



HBM4EU

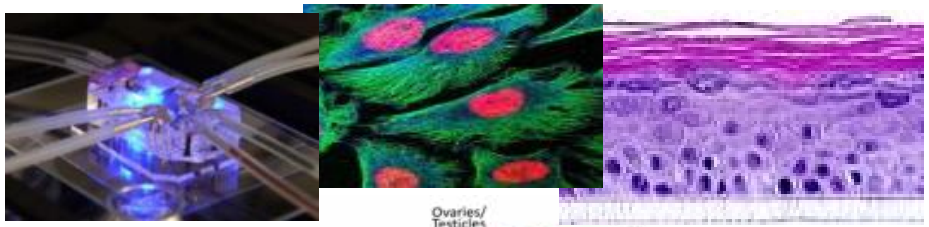
human biomonitoring

integration

High Throughput Screening

European Commission

The modern safety assessment toolbox



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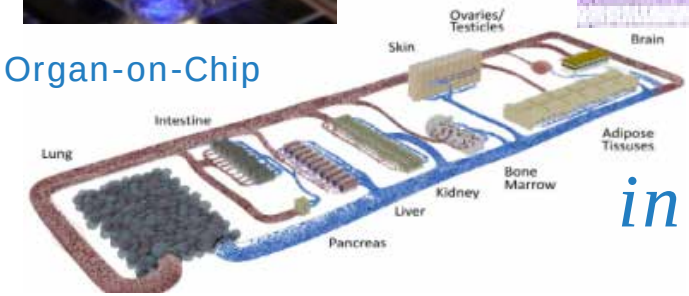

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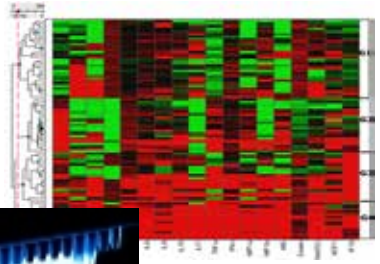
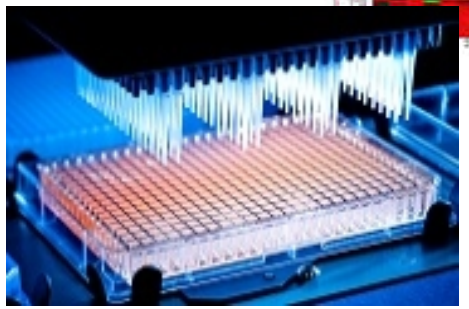
New Approach Methodologies (NAMs)

clinical data

existing animal data

'omics





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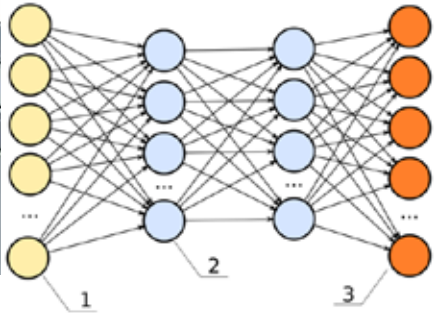
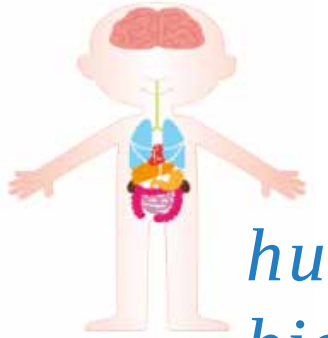


integration

biokinetics



HBM4EU

human biomonitoring

High Throughput Screening

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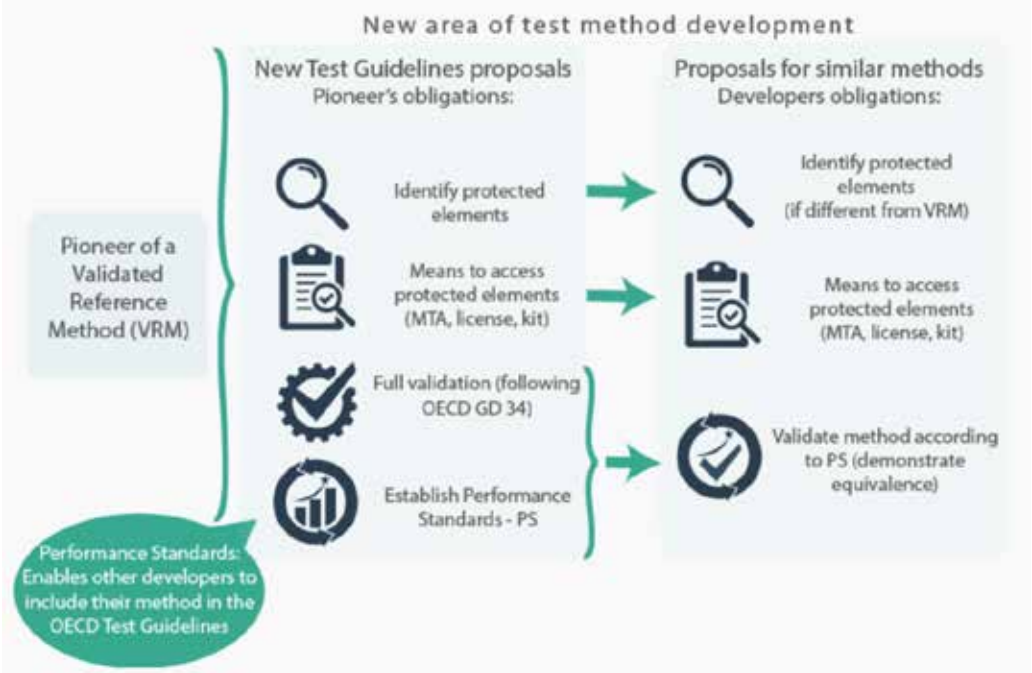
Transparency: OECD policy for confidential information in candidate Test Guidelines

- Method developers encouraged to use other means than confidentiality to protect their intellectual property
- OECD will host confidential information on a protected webpage accessible to National Coordinators only during Test Guideline development
- Once the Test Guideline is adopted, this information will be made publicly available



Source: https://www.oecd.org/chemicalsafety/testing/intellectual-property-in-oecd-test-guidelines.htm

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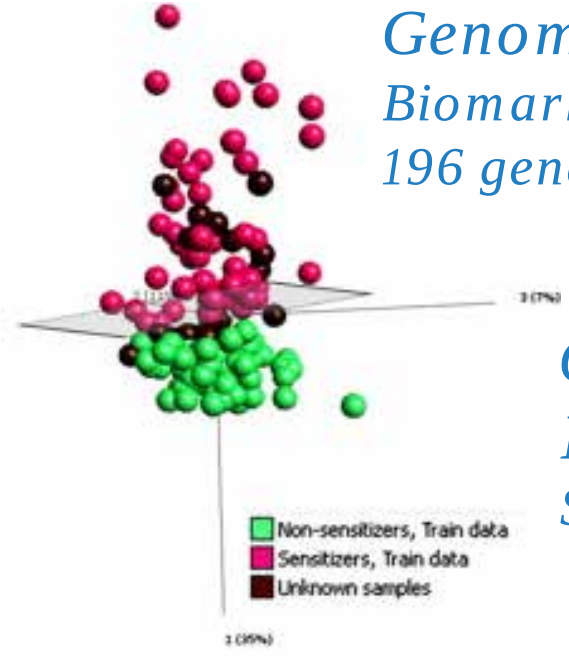
Independent scientific review

- Important part of confidence building process
- Appropriate level of external review depends on the method and context of use
- Might include publication in peer-reviewed journal or review by an independent scientific advisory panel
- International adoption by OECD typically needs formal peer review
- Method developers may fund but should not manage peer review

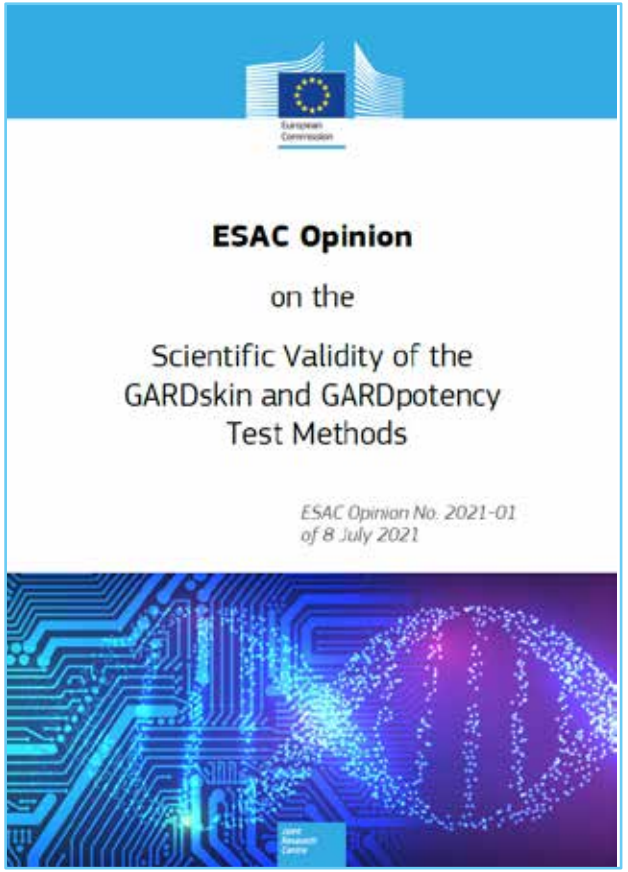
ESAC review of the GARD

Genomic Allergen Rapid Detection (GARDskin)



Genomic based
Biomarker signature
196 genes

Classification based on Machine Learning algorithm
Support Vector Machine



https://ec.europa.eu/jrc/en/science-update/machine-learning-and-omics-arrive-field-regulatory-toxicology

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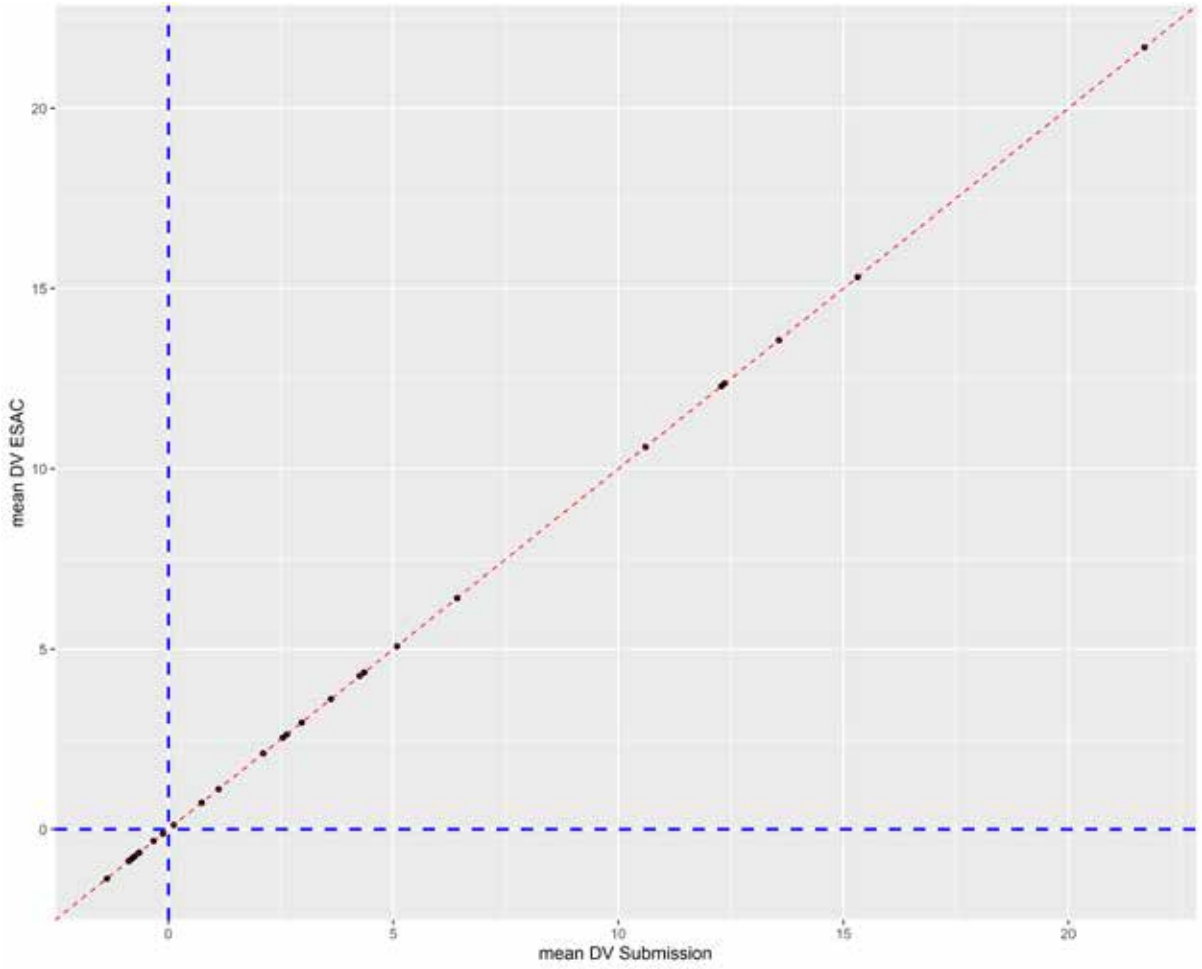
Transparency

Independently reproduce data

- External implementation and training of the models
- Processing of the raw data
- Replicate predictions obtained in the validation study



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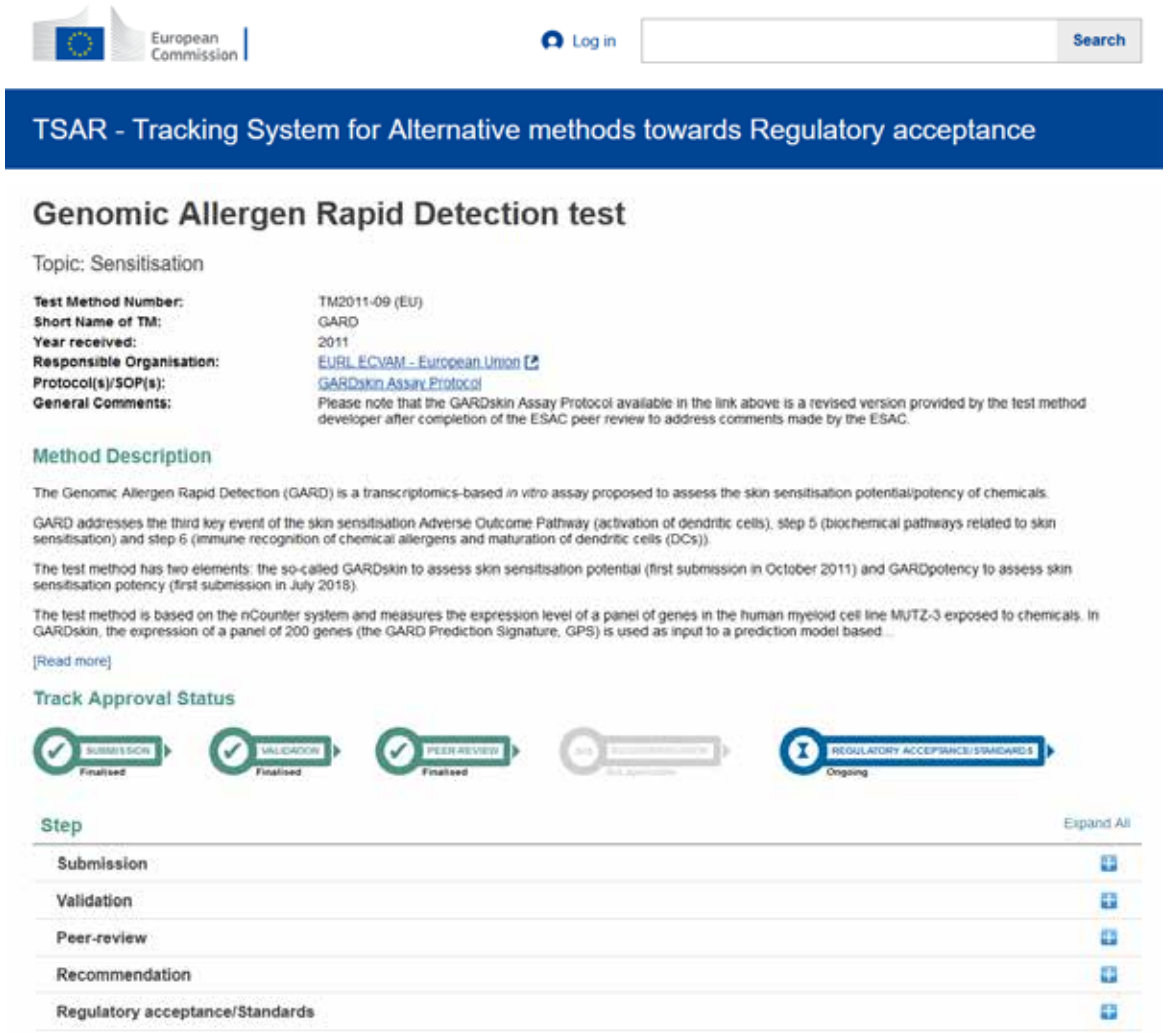
TSAR - Tracking System for Alternative methods towards Regulatory acceptance

Communicate transparently and, as far as possible, make information publicly available



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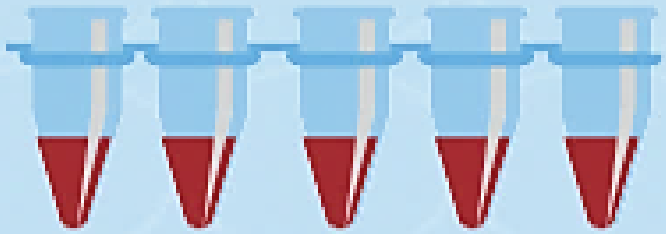
Data integrity in validation studies

- According to OECD GD 34, validation studies should follow the principles of GLP
- Mostly not done in the past but not a problem because studies were coordinated by independent parties
- Now managed by commercial parties
  à trustworthiness becomes questionable
- Important to demonstrate the integrity and credibility of the results, from the raw data through to the final report

Standards to ensure **Reliability** and **Data Integrity**

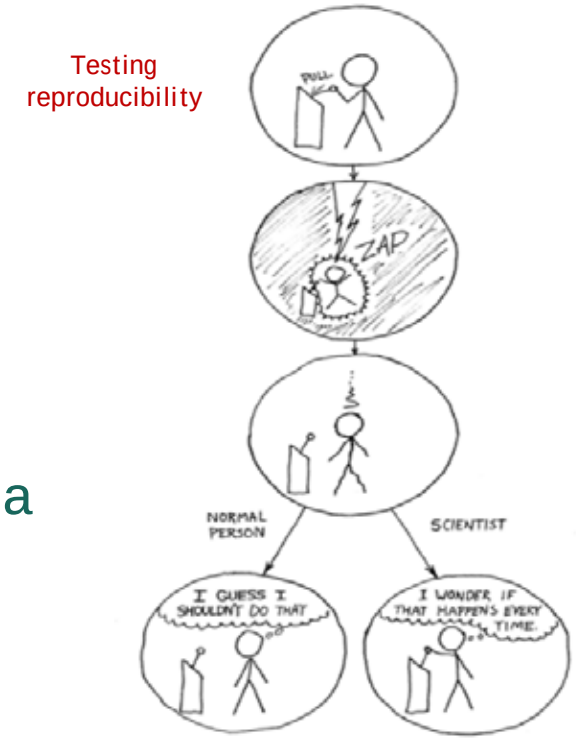


GIVIMP

OECD Guidance Document
on Good In Vitro Method Practices

The OECD has published guidance on Good In Vitro Method Practices (GIVIMP) for the development and implementation of in vitro methods for regulatory use in human safety assessement

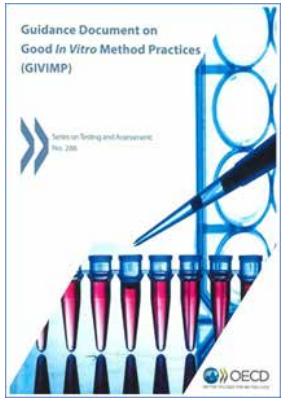
Reproducibility and ring trials



- Demonstrating reproducibility is essential
- Ring trials are the most time-consuming and expensive part of a validation study and are often more a reflection of laboratory quality or expertise than of a NAM's reproducibility
- Assessing BLR is not always possible (e.g. for certain types of technology) and not necessary with automation
- Properly designed training and transfer studies are essential and informative
- Better characterisation of method reproducibility and critical steps by developer, e.g. sensitivity analysis of all parameters that can affect result
- Proficiency testing adds confidence on capacity of a laboratory to perform test

Thyroid Validation Study, a collaborative effort!

14 method developers



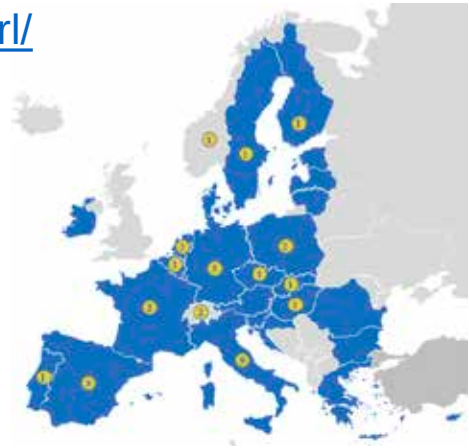
18 Methods

scientific experts

1. University of Pisa, Pisa, Italy.
2. Karolinska Institutet, Solna, Sweden.
3. OECD, Paris, France.
4. National Museum of Natural History, Paris, France.
5. Bayer AG, Wuppertal, Germany.
6. US Environmental Protection Agency, Durnham, USA.
7. Masaryk University, Brno, Czech
8. Republic. University of Antwerp, Antwerp, Belgium.
9. Charité-Universitätsmedizin, Berlin, Germany.
10. University of Catania, Catania, Italy.
11. Syngenta, Cambridge, United Kingdom.
12. German Federal Institute for
13. Risk Assessment, Berlin, Germany.
14. Health Canada, Ottawa, Canada

15 EU-NETVAL labs

https://ec.europa.eu/jrc/en/eurl/ecvam/alternative-methods-toxicity-testing/eu-netval



PART 1: Method Definition & Reliability

- ü Produce SOPs
- ü Method optimization if needed
- ü Aim: assessing robustness and reliability
- ü Experimental study of 5 valid runs

PART 2: Relevance

- ü Aim: assessing overall relevance
- ü Testing of 30 blind-coded chemicals
- ü Experimental study of 3 valid runs

TRACKING SYSTEM FOR ALTERNATIVE METHODS TOWARDS REGULATORY ACCEPTANCE

TSAR tracks the progress of alternative, non-animal methods, for testing chemicals or biological agents such as vaccines towards acceptance as a recognised test method for use in various sectors

TSAR

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Final thoughts

- Validation as a process of building scientific confidence is essential to facilitate acceptance and ensure sound science-based decisions
- Validation needs to keep pace with rapid scientific progress, e.g. emergence of Defined Approaches (data integration), computational models, new technologies such as Organ-on-Chip
- Important to maintain scientific integrity, credibility and usefulness while making process more efficient
- Frame validation as a process to characterize and reduce uncertainty rather than a ring trial to demonstrate "toxicological equivalence"
- Validation ≠ regulatory acceptance and use

Thank you

European Commission