# The European Union Reference Laboratory for Alternatives to Animal Testing

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EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

**Institute for Health and Consumer Protection**
**DG Joint Research Centre**

AIMBE/NIH Workshop

March 2014

Joint Research Centre

# Talk Outline

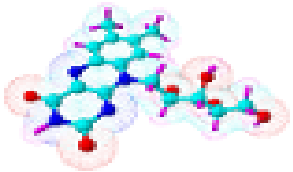
*Validation of new tools …*

- Overview of EURL ECVAM
- Validation in a regulatory context
- Validation in a research context

# Our EU Policy focus

## *Regulation of Chemicals and the Protection of Animals*

- Animal-free methodology to assess the hazard posed to consumers, workers and the environment
- Industrial chemicals, cosmetic ingredients, food constituents, pesticides, biocides and drugs
- Advancing safety assessment science to support regulatory decision making



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DG JRC - Institute for Health and Consumer Protection

# Systems Toxicology Unit / EURL ECVAM

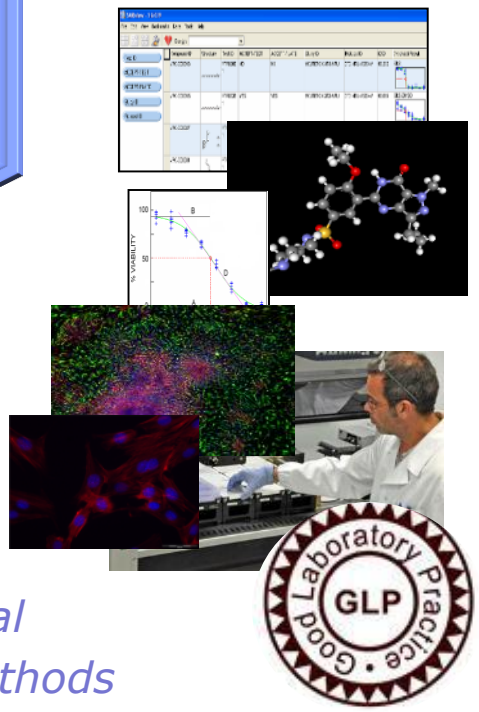
*75 staff*

Groups

- Assay Validation
- Predictive Toxicology
- Toxicity Pathways

Facilities

- In Vitro GLP
- HTS HCS




## Projects

*Integrated approaches to testing and assessment*

*Standardisation and international harmonisation of alternative methods*

*Combined exposures and chemical mixtures*

*Endocrine disruptors*

*Information systems for safety assessment and alternative methods*

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20.10.2010 EN Official Journal of the European Union L 276/33

# DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

## of 22 September 2010

## on the protection of animals used for scientific purposes

"While it is desirable to replace the use of live animals in procedures by other methods not entailing the use of live animals, the use of live animals continues to be necessary to protect human and animal health and the environment. However, **this Directive represents an important step towards achieving the final goal of full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible** to do so. To that end, it seeks to facilitate and promote the advancement of alternative approaches."



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Established under the Directive 2010/63/EU on the protection of animals used for scientific purposes

# The European Union Reference Laboratory for Alternatives to Animal Testing

## Key responsibilities*

- Coordinate and promote development and use
- Coordinate validation at Union level
- Information exchange on development
- Databases and information systems
- Promote dialogue between legislators, regulators, and stakeholders

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

*Article 48 of the Directive, Annex VII

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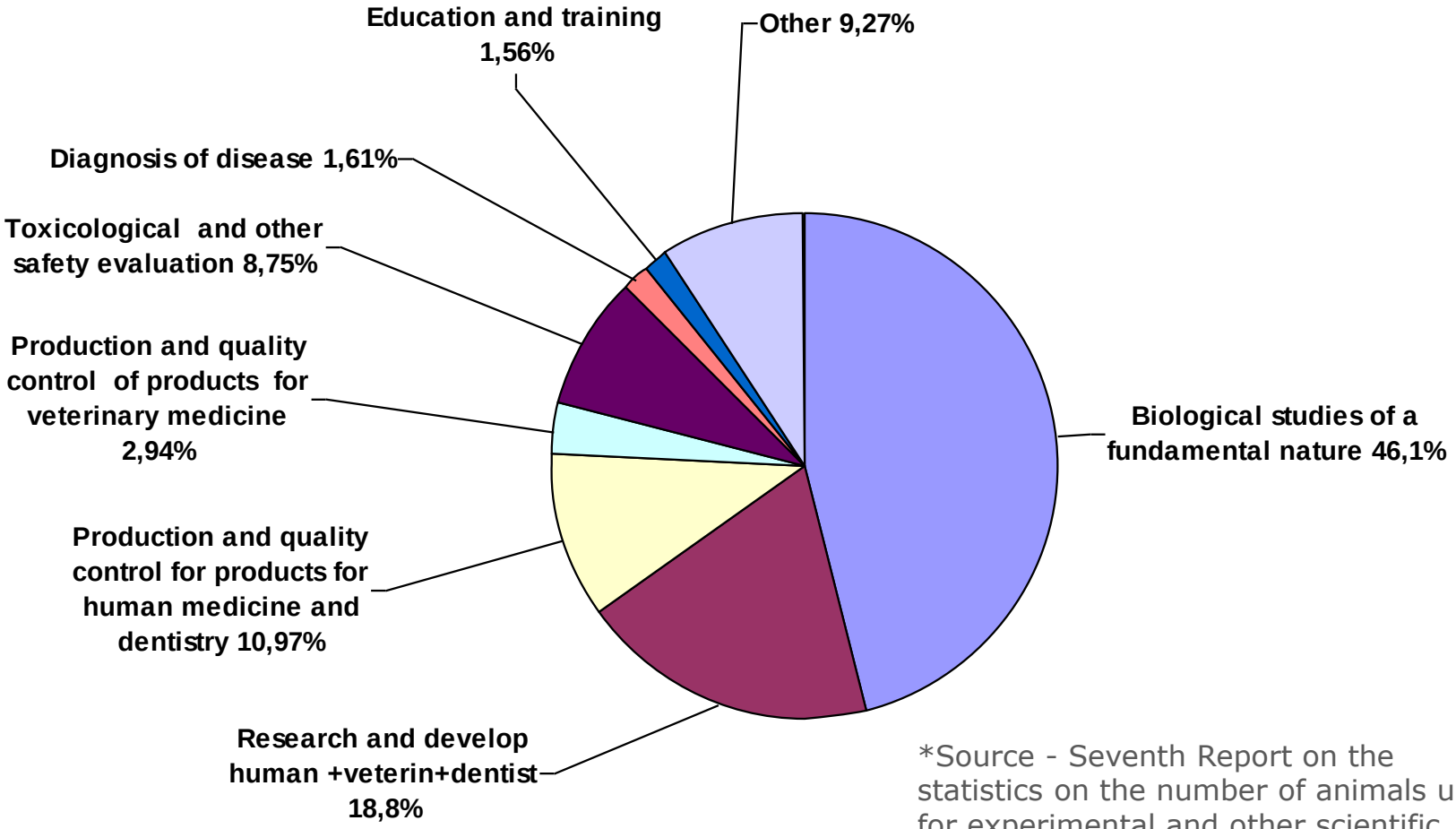
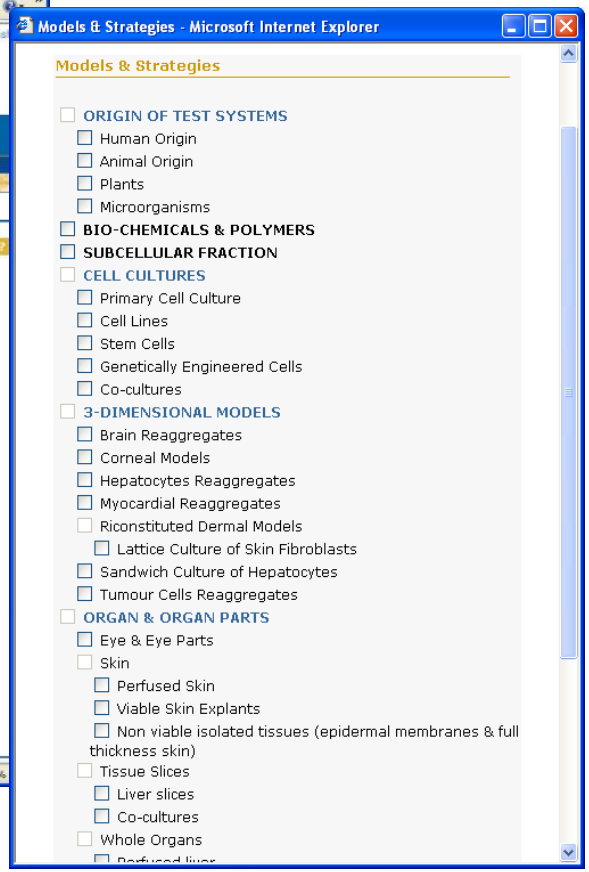
# *Statistics on the purposes of the procedures carried out in the 27 Member States in 2011**




*Source - Seventh Report on the statistics on the number of animals used for experimental and other scientific purposes in the EU MS (in preparation)

# ECVAM DataBase service on ALternative Methods

## DB-ALM


**http://ecvam-dbalm.jrc.ec.europa.eu**

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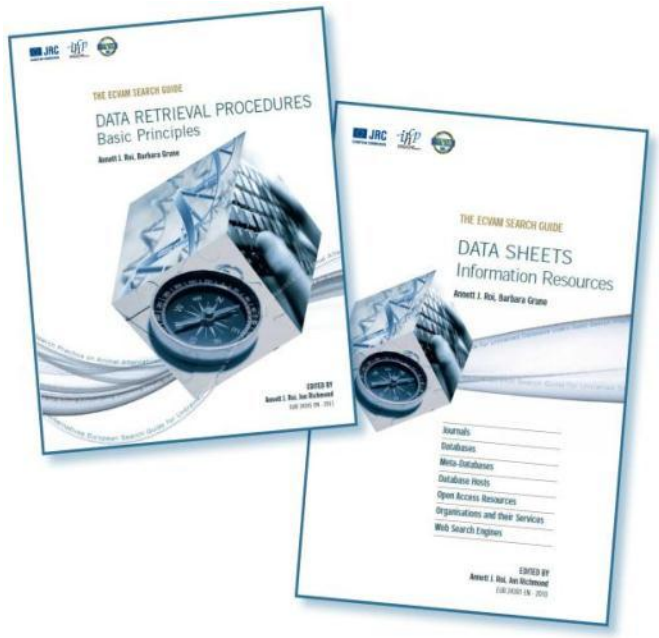
# Promoting a broader use of alternatives

## EURL ECVAM Search Guide

- Search principles & procedures, terms and guidance
- 7-step check list to ensure comprehensive searches
- Inventory of key resources

**Support to project authorisation process for animal experiments**

(Directive 2010/63/EU)

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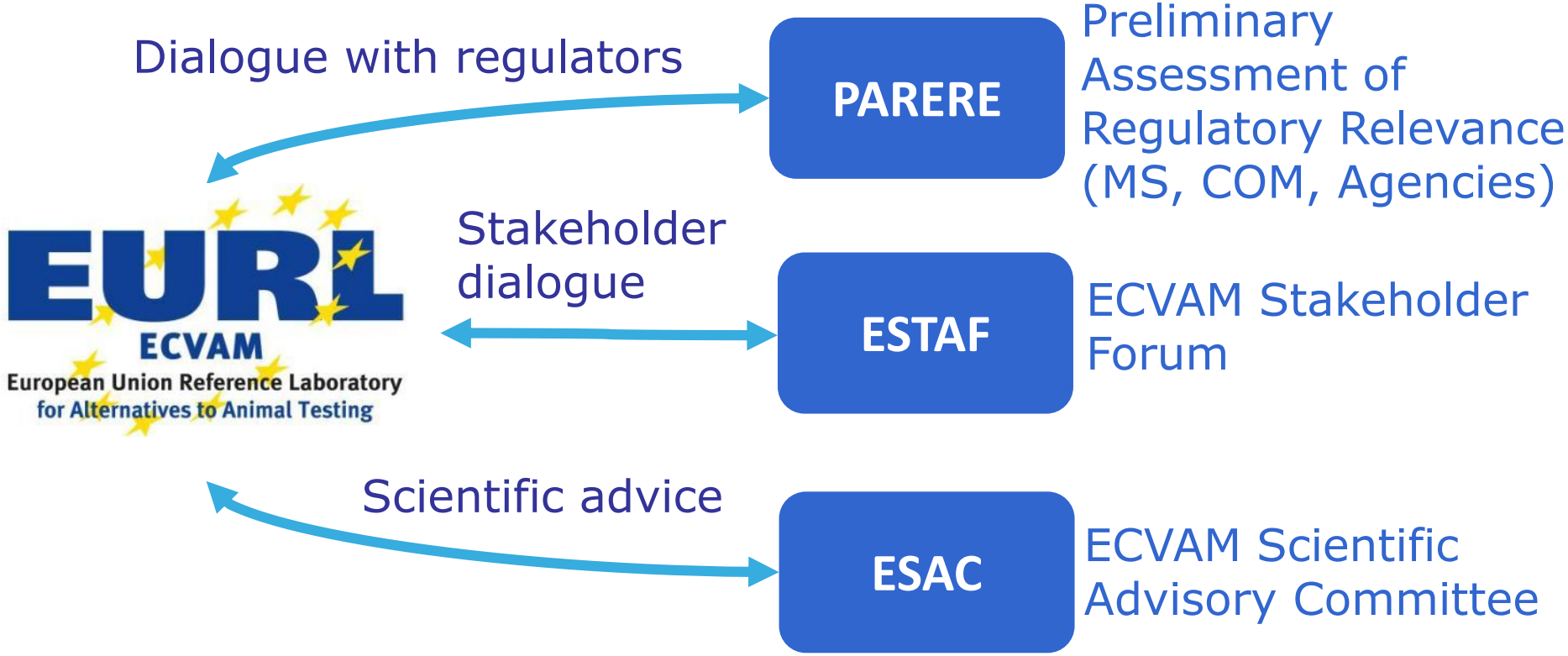
# EURL ECVAM interactions with regulators, stakeholders and scientific advisors

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# ICATM

## International Cooperation on Alternative Test Methods

- Founded in 2009 by JaCVAM (Japan), NICEATM-ICCVAM (USA), EURL ECVAM (EU), Health Canada, and KoCVAM (Republic of Korea). Recent interest from BraCVAM (Brazil). Contacts with China.
- Working together at every step of the process:
  Evaluation of Promising Methods; Design and Execution of Validation Studies, Peer Review, Recommendations, Development of Int. Guidance and Guidelines, Dissemination).
- Latest Meeting in November 2013 led to a number of solid outcomes and actions.

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# Talk Outline

*Validation of new tools …*

- Overview of EURL ECVAM
- Validation in a regulatory context
- Validation in a research context

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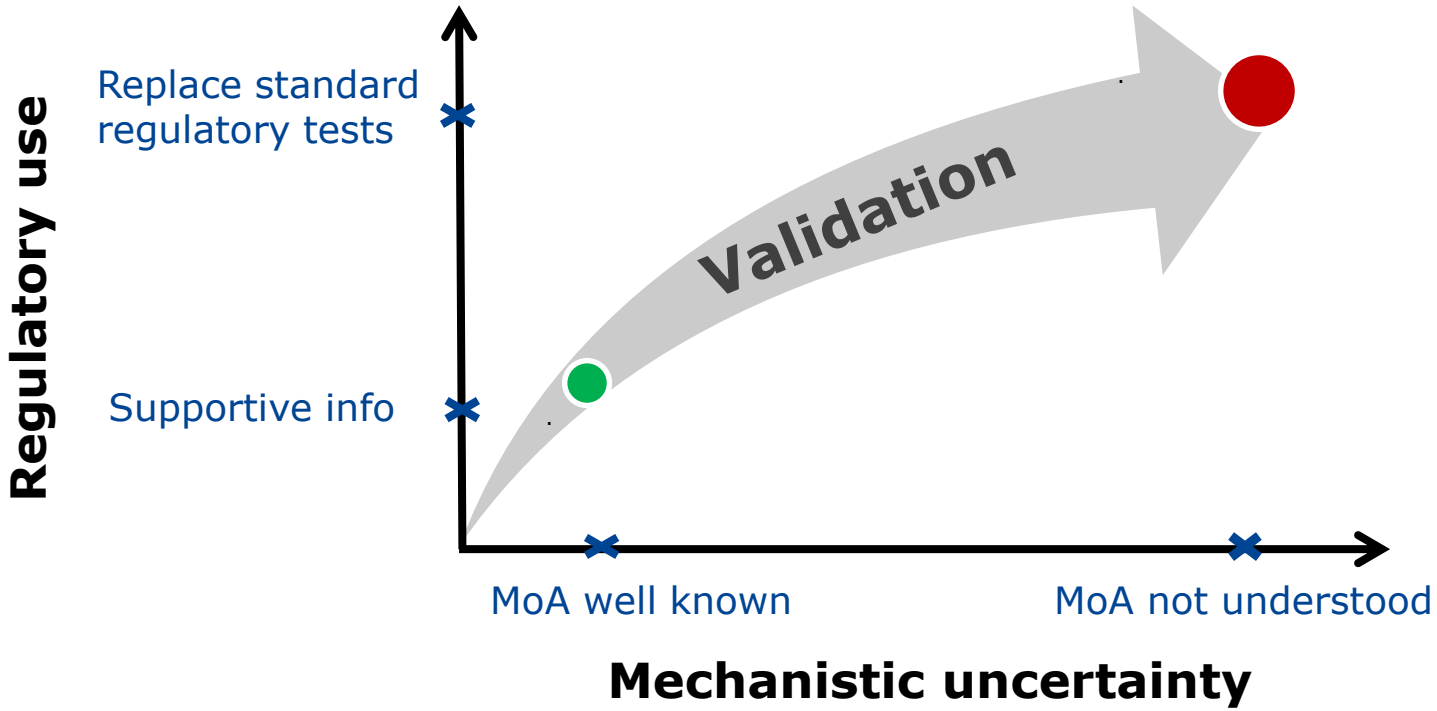
# Approaches to validation depend on context




## *3Ps of Validation: Principles, Purpose and Process*

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## Consultation

## Validation Work Flow

## Records

**ICATM:** Exchange info. on promising methods. Decide how to collaborate

**PARERE & ESTAF:** Initial assessment of relevance and utility

**1. Assessment of submitted method**
Evaluate status and prioritise

*Test Submission*

*Evaluation report*

**ICATM:** Review aspects of VS. Propose VMG members and observers

**Ad hoc consultations:** On study design and related information

**2. Undertake Validation Study**
Characterise reliability and relevance

*Validation Study Plan*

*Validation Report*

**ICATM:** Proposal of experts & observers for ESAC WGs

**3. Independent Peer Review**
ESAC assessment of study and outcome

*ESAC Request*

*ESAC report & Opinion*

**ICATM:** Input to strengthen claims and achieve harmonisation/impact

**PARERE, ESTAF, ICATM, Public, Test submitter**

**4. ECVAM Recommendation**
Propose uses and further steps

*EURL ECVAM Recommendation With Annexes*

*Recorded comments*

*Submitter Response*

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# JOINT RESEARCH CENTRE

## Institute for Health and Consumer Protection (IHCP)

> Our Reference Centres a

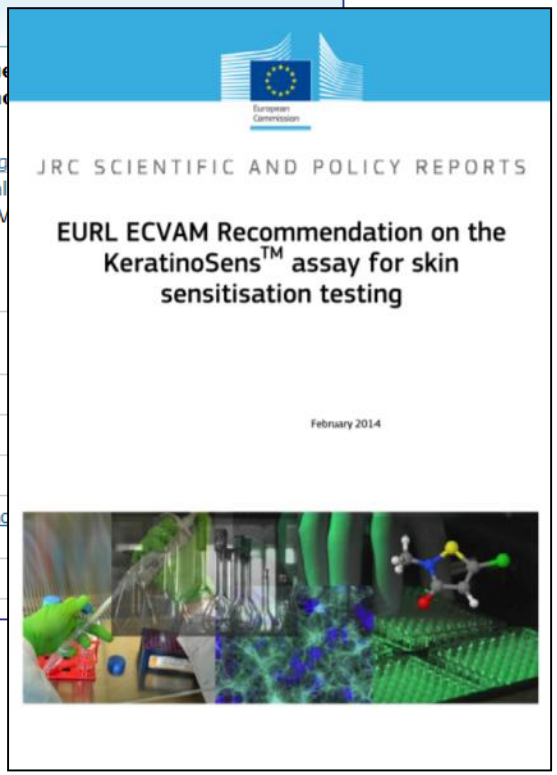
http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/eurl-ecvam-recommendations

## EURL ECVAM Recommendations

**The aim of an EURL ECVAM Recommendation is to provide EURL ECVAM views on the validity of the test method in que regulatory applicability, limitations and proper scientific use of the test methods, and to suggest possible follow-up a knowledge gaps.**

During the development of its Recommendation EURL ECVAM consults with its consultation body for Preliminary Assessment of Reg its EURL ECVAM Stakeholder Forum (ESTAF). Moreover, EURL ECVAM consults with other Commission services and its international of the International Collaboration on Alternative Test Methods (ICATM). Moreover, before finalising its recommendations, EURL ECV general public and, if applicable, from the test method submitter.

| Health / environmental endpoint | Recommendation |
|---|---|
| Skin Sensitisation | KeratinoSens™ assay for Skin Sensitisation testing |
| Carcinogenicity | Cell Transformation Assay for carcinogenicity testing based on the Bhas 42 cell line |
| Skin Sensitisation | Direct Peptide Reactivity Assay (DPRA) |
| Acute Oral Toxicity | 3T3 NRU Assay for Supporting the Identification of Substances Not Requiring Classification for Ac Toxicity |
| Carcinogenicity | Three Cell Transformation Assays for in vitro Carcinogenicity Testing |

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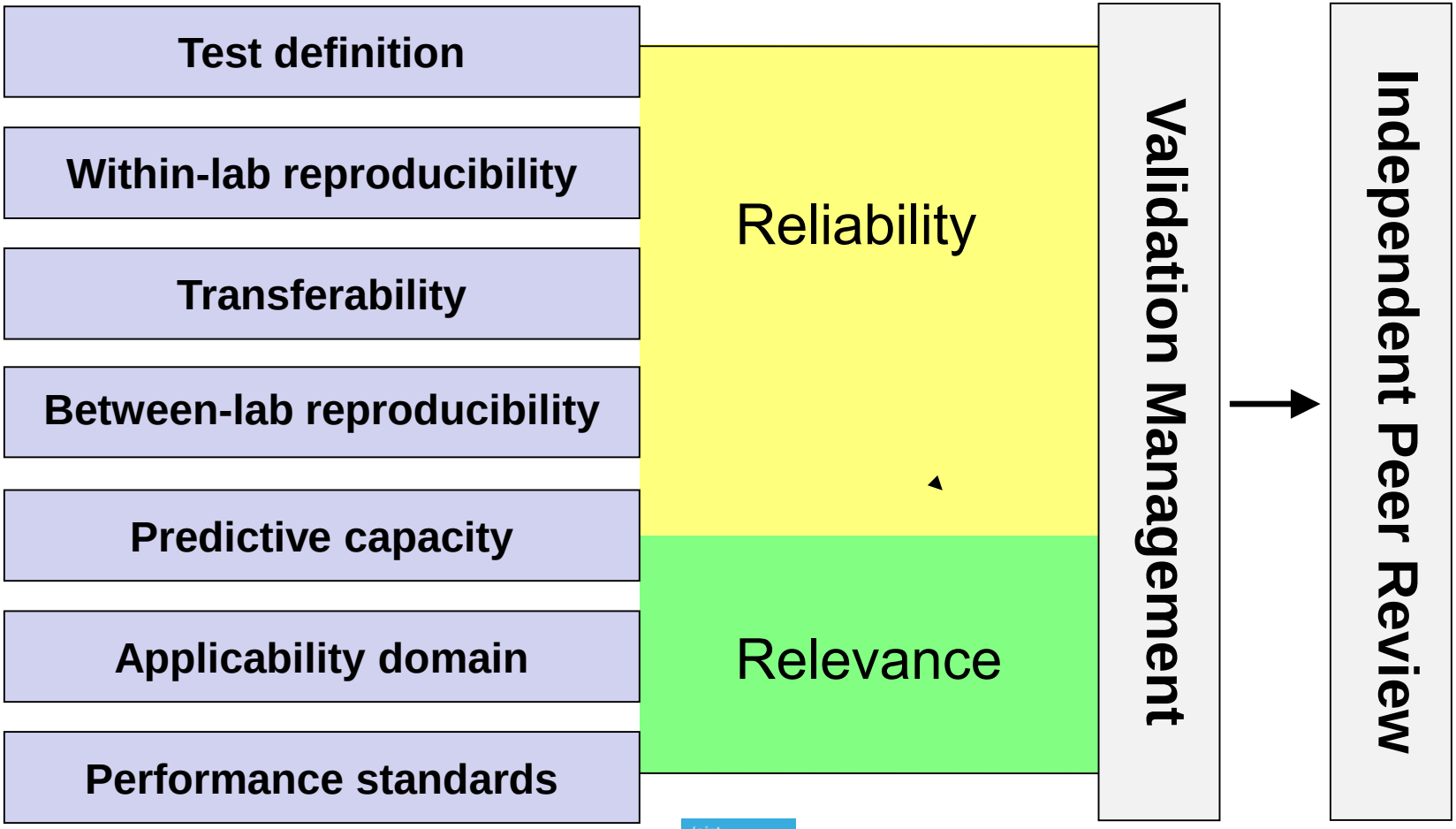
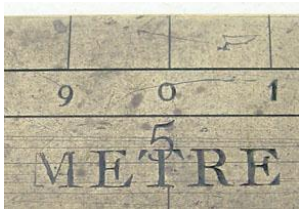
# Validation – *a modular approach*




*Hartung et al, 2004*



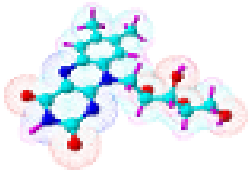

# Validation towards Standards

**Reporting STD**: For ***describing a method*** and the ***results obtained*** from it for a particular test item.

**Physical STD:** Reference chemicals with clearly defined structural, physiochemical, mechanistic, toxicological and toxicokinetic properties.

**Methodological STD**: Protocols to characterise a method using physical STD to derive information on ***basic performance*** and ***application-specific*** performance.

*Underway – Project to develop STD for AR Transactivation Assays*
*Coming soon! Project to develop STD for TK/Clearance methods (inc. web-based survey of methods)*



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uropean Commission > JRC > IHCP > Our Reference Centres and Laboratories > EURL ECVAM (European Union Reference Laboratory for Alternatives to Animal

- EURL ECVAM (European Union Reference Laboratory for Alternatives to Animal Testing)
- Latest News
- About EURL ECVAM
- New to EURL ECVAM?
- EURL ECVAM's Validation Process
- Test Method Submission
- Validation & regulatory acceptance
- EURL ECVAM Recommendations
- EURL ECVAM Strategy Papers
- Advisory and Consultation Bodies
- **EU-NETVAL (European Union Network of Laboratories for the Validation of Alternative Methods)**
- Laboratories & Research
- International collaboration

## EU-NETVAL (European Union Network of Laboratories for the Validation of Alternative Methods)

**EU-NETVAL**'s mission is to provide support for EURL ECVAM validation studies that serve to assess the reliability and relevance of alternative methods that have a potential to replace, reduce, or refine the use of animals for scientific purposes.

EU-NETVAL will be coordinated and sustained by the EURL ECVAM, in close collaboration with Directorate-General for Environment (to ensure interactions with the National Contact Points for implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes).

EU-NETVAL was set up by EURL ECVAM in response to the provision of Directive 2010/63/EU on the protection of animals used for scientific purposes which requests that EU Member States assist the European Commission in the validation of alternative methods. Currently there are a total of **26 members of EU-NETVAL**, selected against pre-defined eligibility criteria (including **25 test facilities** from EU Member States plus the European Commission's own *in vitro* GLP test facility operated by EURL ECVAM, which coordinates the network) and approved by the National Contact Points.

The Terms of Reference for EU-NETVAL detail the legislative anchor, the establishment of the network and the maintenance of its membership, tasks of network members and of EURL ECVAM in support of validation studies, the allocation of tasks to members and the financing of network activities.

Application for membership of EU-NETVAL is currently closed. A new call for members is anticipated during 2014/2015.

For further information on EU-NETVAL please contact us at JRC-ECVAM-NETVAL@ec.europa.eu

http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/eu-netval

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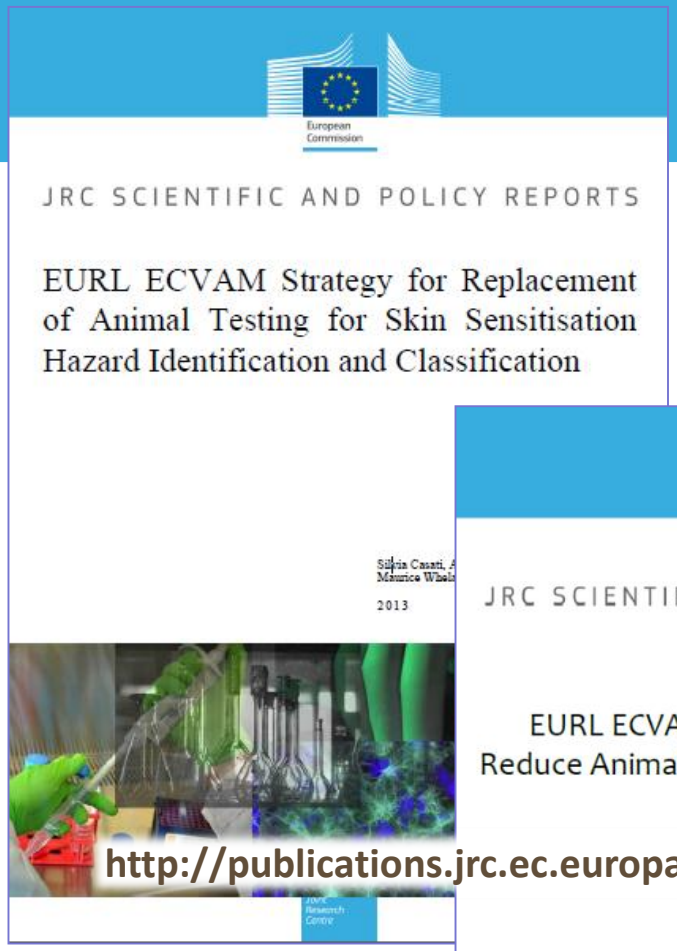


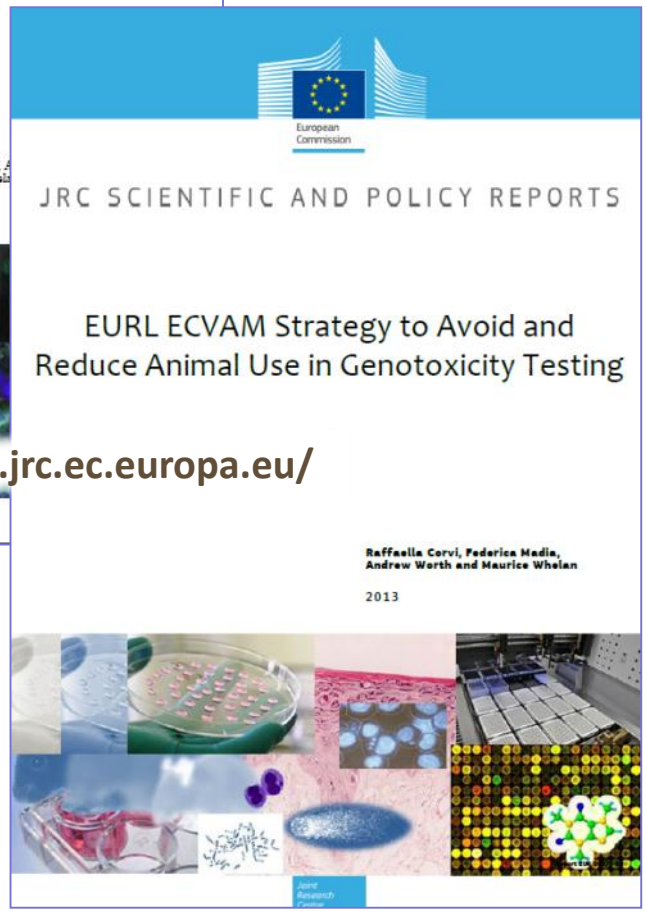


http://publications.jrc.ec.europa.eu/

*In preparation*

- *Acute Toxicity*
- *(Dev)Neurotoxicity*
- *Biokinetics*
- *Fish Toxicity*
- *….*

- Analysis of regulatory information needs
- Cross-sectorial scope
- Broad strategic aims
- Ambitious but pragmatic
- Solutions intended for regulatory acceptance
- Look towards international TGs and Guidance (IATA - Integrated Approaches to Testing and Assessment )

*Explicit*
*Transparent*
*Inclusive*

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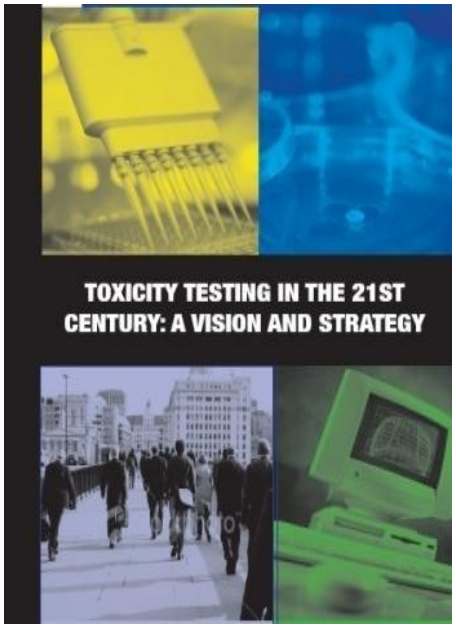
# Toxicity Pathways (NRC 2007)





WHO/IPCS Mode-of-Action Framework (Meek et.al. 2013)

Adverse Outcome Pathways (Ankley et. al. 2010)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# Mechanistic Relevance
# *- Adverse Outcome Pathways*

- Being explicit about toxicological ***mode of action***


- to rationally design ***integrated prediction systems***
- fit for the purpose of ***supporting safety decisions***

*… facilitating a shift towards a knowledge-driven paradigm for chemical risk assessment*

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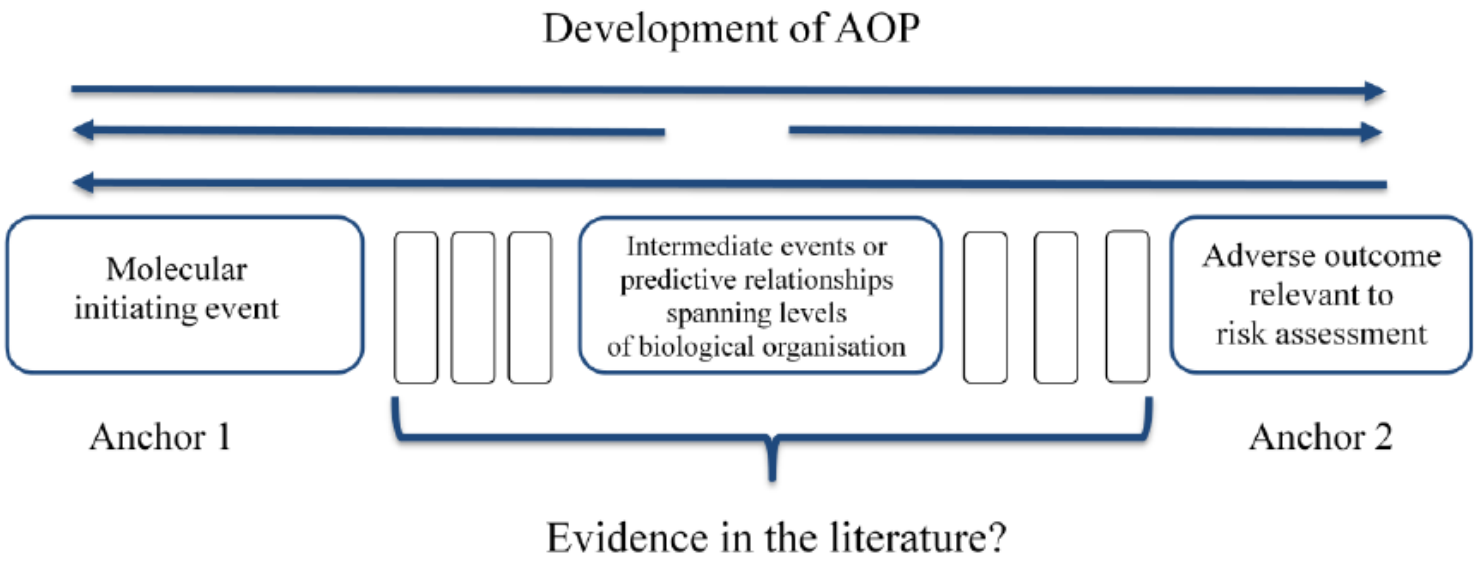
# OECD

## Adverse Outcome Pathway Development Programme

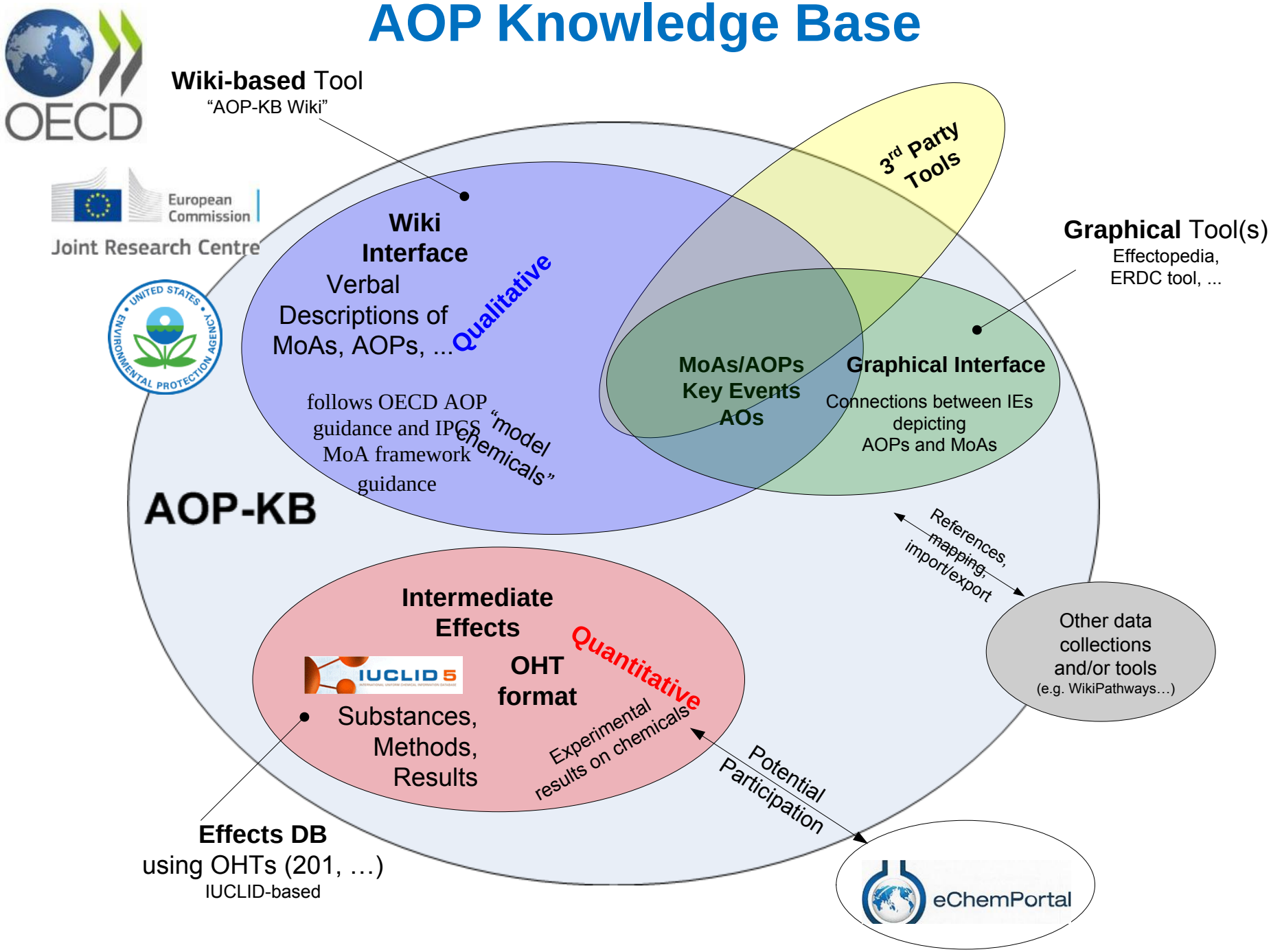
*Extended Advisory Group on Molecular Screening and Toxicogenomics*

Co-chairs: Robert Kavlock (US EPA) & Maurice Whelan (EC JRC)




*OECD Template and Guidance on developing and assessing the completeness of Adverse Outcome Pathways (2013)*

# AOP Knowledge Base



# OECD

*Extended Advisory Group on Molecular Screening and Toxicogenomics*

## Guidance for describing non-guideline in vitro test methods to facilitate their consideration in regulatory applications

Introduction to Guidance

1. General information
2. Test Method Definition
3. Data interpretation and prediction model
4. Test Method Performance
5. Potential Regulatory applications
6. Bibliography
7. Supporting information

Glossary of terms

*Work in progress!*

# Talk Outline

*Validation of new tools …*

- Overview of EURL ECVAM
- Validation in a regulatory context
- Validation in a research context

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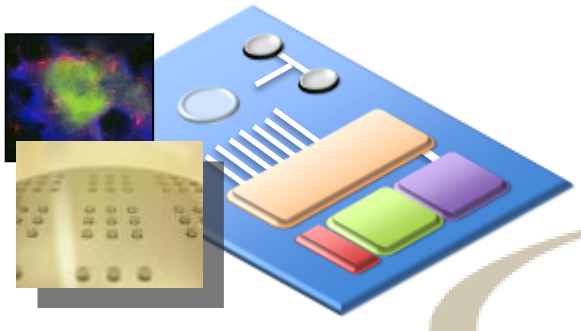
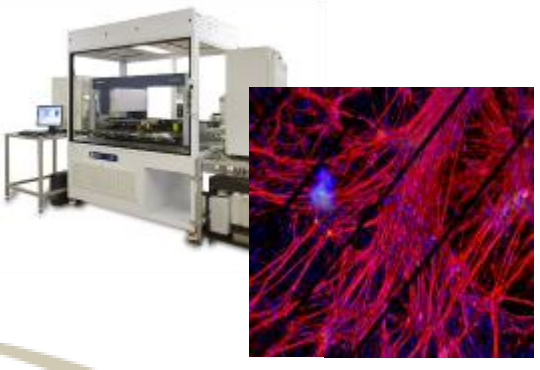
# Safety Assessment Ultimately Replacing Animal Testing

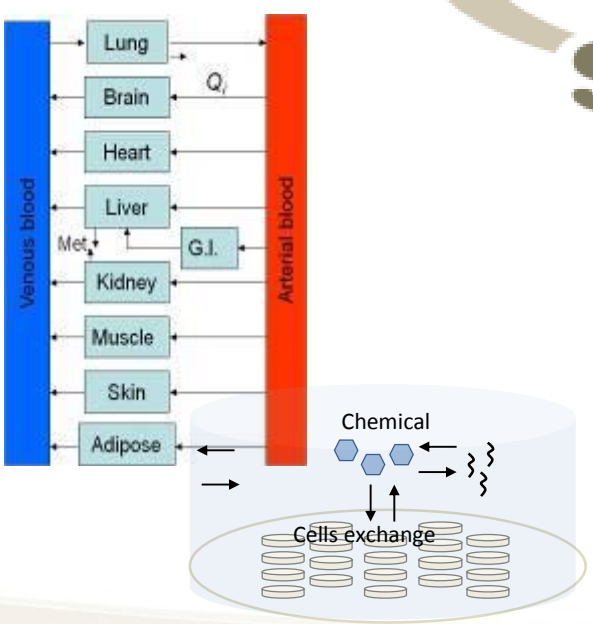

www.seurat-1.eu

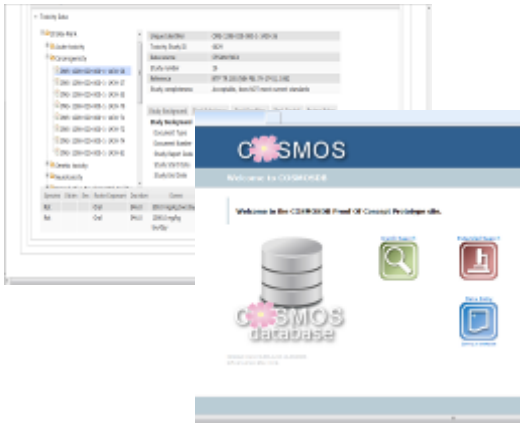
# Scientific Tools

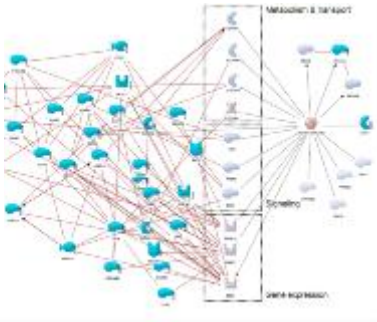


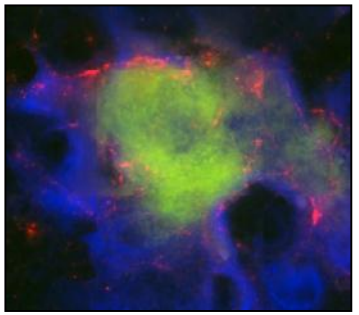



SEURAT-1





*… how to convert them into solutions for safety assessment?*

# SEURAT - The Strategy

*The SEURAT strategy is to adopt a toxicological* ***mode-of-action framework*** *to describe how any substance may adversely affect human health, and to use this knowledge to develop complementary theoretical, computational and experimental (in vitro) models that predict quantitative points of departure needed for safety assessment.*

# Validation - *Proving Concepts*

- Level 1: Knowledge

  Theoretical MoA descriptions, which might be further refined or confirmed based on the outcome from SEURAT-1 activities

- Level 2: Prediction

  Integrated assessment and testing systems for mechanistic grouping of chemicals and for quantitative prediction of adverse effects.

- Level 3: Application

  Application of the information derived from methods and predictive systems to support safety assessment processes and decisions.

# Predictive toxicology – Case studies

| | |
|---|---|
| Prediction Goal | Please clearly indicate the purpose of the system/strategy/method being developed with respect to the toxological effect(s) it is designed to predict. |
| Mechanistic basis | Please describe the mechanistic basis underpinning the approach, mentioning for example any relevant mode(s) of action that are being considered. |
| Scientific approach | Please briefly describe the scientific approach to be taken including, for example, the design rationale, what methods will be employed, the basis for predicting an outcome and interpretation of data, and, if foreseen, any anticipated validation activity to assess predictive performance. |
| Chemical selection | Please identify what chemicals you intend to use for development and assessment of the system, including, for example, positive and negative reference chemicals. |

**9 case studies defined – deliver Q1 2015 !**

# *Prediction Goal - designing for purpose*

- Profile the bioactivity of a chemical to associate it with an activity category that is related to a toxicity endpoint.
- Identify a chemical as being associated, or not, with a MoA that is likely to cause an adverse health outcome.
- Rank chemicals within a bioactivity/MoA category with respect to their potency/likelihood to cause toxicity.
- Predict a quantitative *in vivo* point-of-departure for a chemical with respect to a specific toxicity endpoint.

# Case studies on *Application* Level

- **DATA RICH**

  Make use of information from the SEURAT-1 *in vitro* molecular screening and 'omics data, as well as computational models to strengthen the weight of evidence approach and to improve the robustness of a read-across or chemical categorisation and validating the case.

- **DATA POOR**

  *An ab initio* assessment using the Integrated Assessment Strategy developed by SEURAT-1 that would highlight gaps for future development and illustrate overall progress made in SEURAT-1.

# Predictive but Pragmatic

# In summary …

Validation is a fundamental part of the scientific process

…. *but be scientific, smart, and purpose driven*

Innovation is indeed needed,

as an evolution not revolution,

to avoid ….

http://vickybeeching.com/blog/wp-content/uploads/2012/02/baby-out-with-bath-water.jpeg

# Thank you !

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