A path to validation – SEURAT-1 case studies and the role of ECVAM

Elisabet Berggren

ToxBank Public Forum, London, 26 October 2015

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

Joint Research Centre

DG Joint Research Centre - JRC the Commission's in-house science service

Institute for Reference Materials and Measurements

IRMM

IET

Institute for Energy and Transport

HQ

Headquarters

ITU

Institute for Transuranium Elements

Petten

Geel

Brussels

Karlsruhe

Ispra

IPTS

Institute for Prospective Technological Studies

Seville

IHCP

Institute for Health and Consumer Protection

IPSC

Institute for the Protection and Security of the Citizen

ISM

Ispra Site Management

IES

Institute for Environment and Sustainability

IHCP (Institute for Health and Consumer Protection), Ispra

European Union Reference Laboratory for alternatives to animal testing

IHCP Directorate

EURL ECVAM European Union Reference Laboratory for Alternatives to Animal Testing

- Chemical Assessment and Testing
- Public Health Policy Support
- Molecular Biology and Genomics
- Nanobio-sciences
- Systems Toxicology *Head of Unit: Maurice Whelan*

Joint Research Centre

Directive 2010/63/EU: Protection of animals used for scientific purposes

AIM:

Improve the welfare of those animals still needed to be used, as well as to firmly anchor the principle of the 3 Rs, to Replace, Reduce and Refine the use of animals.

MEASURES:

- Animal experiments are restricted to certain purposes
- Only certain types of animals can be used
- Authorisation of breeders, suppliers and users
- Avoidance of duplication and promoting alternative methods
- Establishment of a Union Reference Laboratory

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European Union Reference Laboratory for Alternatives to Animal Testing

objectives:

PREDICT

adverse outcome or disease in human caused by a chemical disturbing the biological system based on systems knowledge and integrated assessment and testing methods

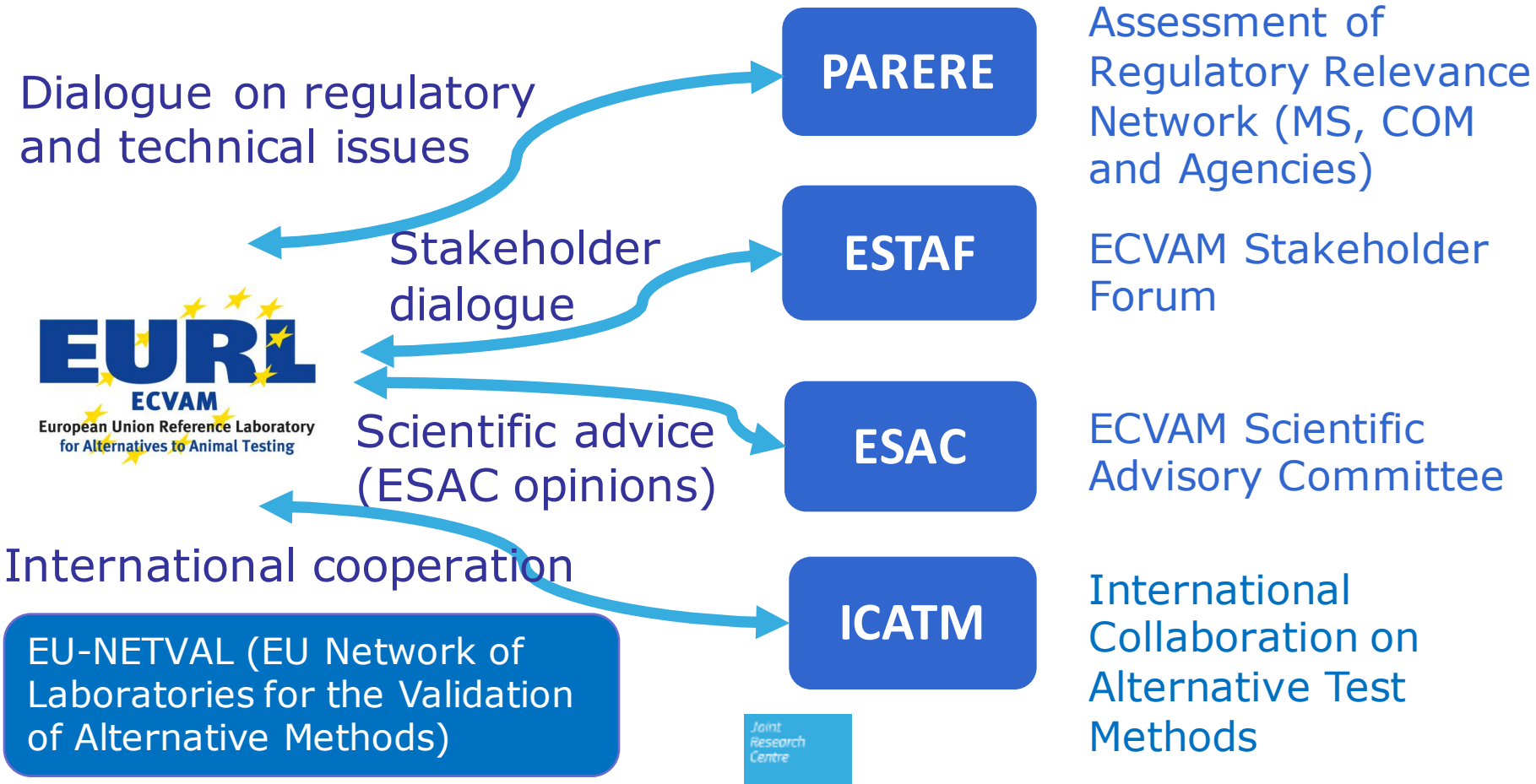
VALIDATE

new in vitro methods to be applied in integrated safety assessment and identify the methods that best will contribute to testing strategies leading to full replacement

DISSEMINATE

knowledge of alternative methods and their application to promote more efficient safety assessment of chemicals and to better support the 3R principle in all scientific research

We try to promote dialogue between legislators, regulators, and stakeholders



EURL ECVAM Recommendations & internationally accepted *in vitro* methods

- Skin Irritation TG 439
- Phototoxicity TG 432
- Skin Corrosion TGs 430, 431, 435
- Eye Irritation / corrosion TGs 437, 438, 460, 491, 492
- Toxicokinetics TG 428
- Genotoxicity TGs 471, 473, 476, 487, 490
- Skin Sensitisation TGs 442C, 442D
- Carcinogenicity GD on SHE CTA
- Skin Irritation / Corrosion GD on IATA

OECD

ICH harmonisation for better

VICH

ISO International Organization for Standardization

cen European Committee for Standardization
Comité Européen de Normalisation
Europäisches Kommitee für Normung

EURL ECVAM Databases assisting in finding Alternatives

DB-ALM: EURL ECVAM DataBase service on ALternative Methods

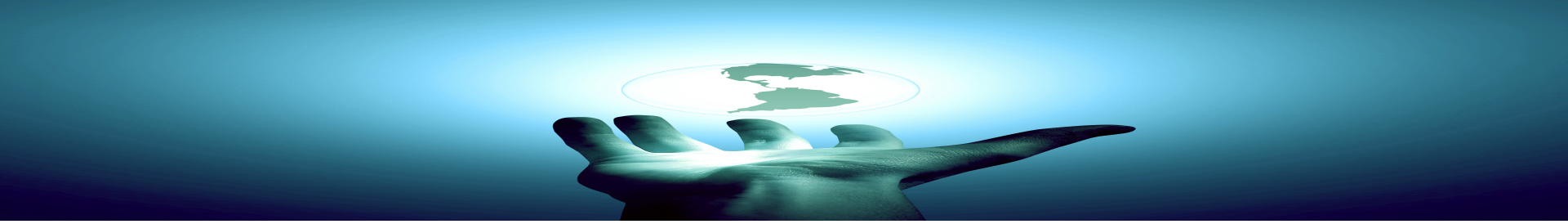
http://ecvam-dbalm.jrc.ec.europa.eu

JRC QSAR Model Database

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

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

Development of more relevant models to human based on current knowledge and technology

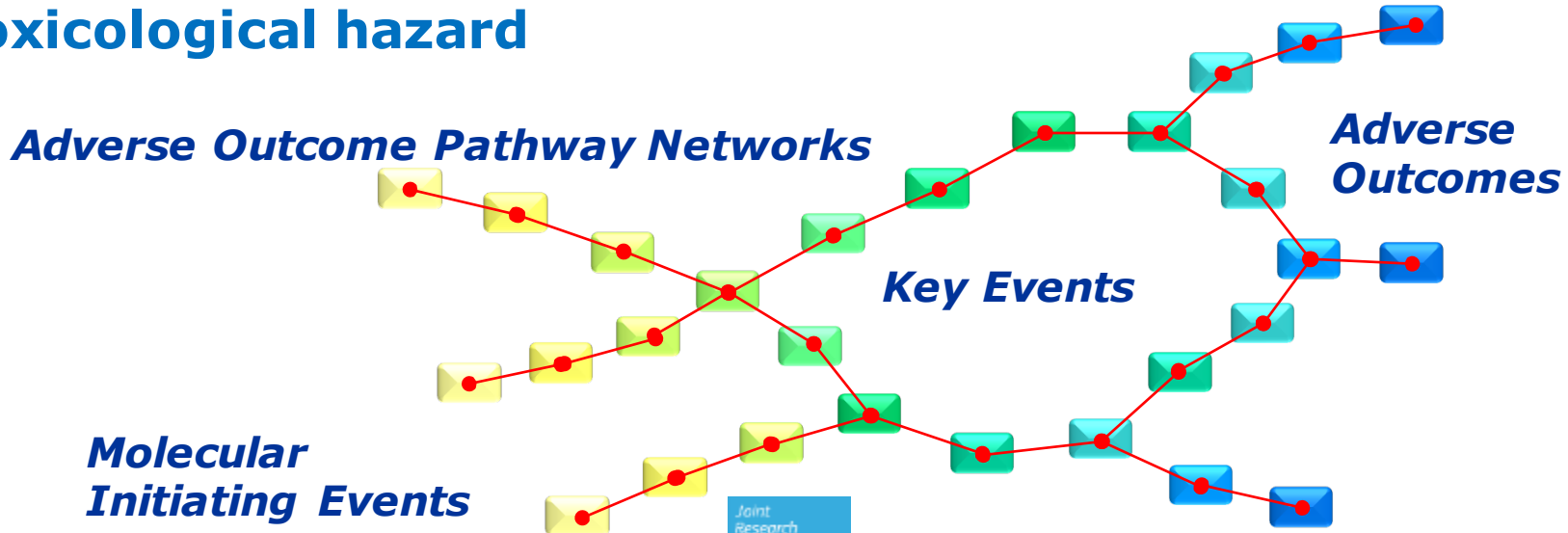


Stimulating innovation towards more reliable but also time and cost efficient approaches

Move away from

-thinking

Transitioning to a new way of describing toxicological hazard



Adverse Outcome Pathways – the systems failure

A description of how a biological systems fails and the necessary conditions that lead to the failure.

It is not therefore a description of the system itself,

but requires understanding of the system in order to be described

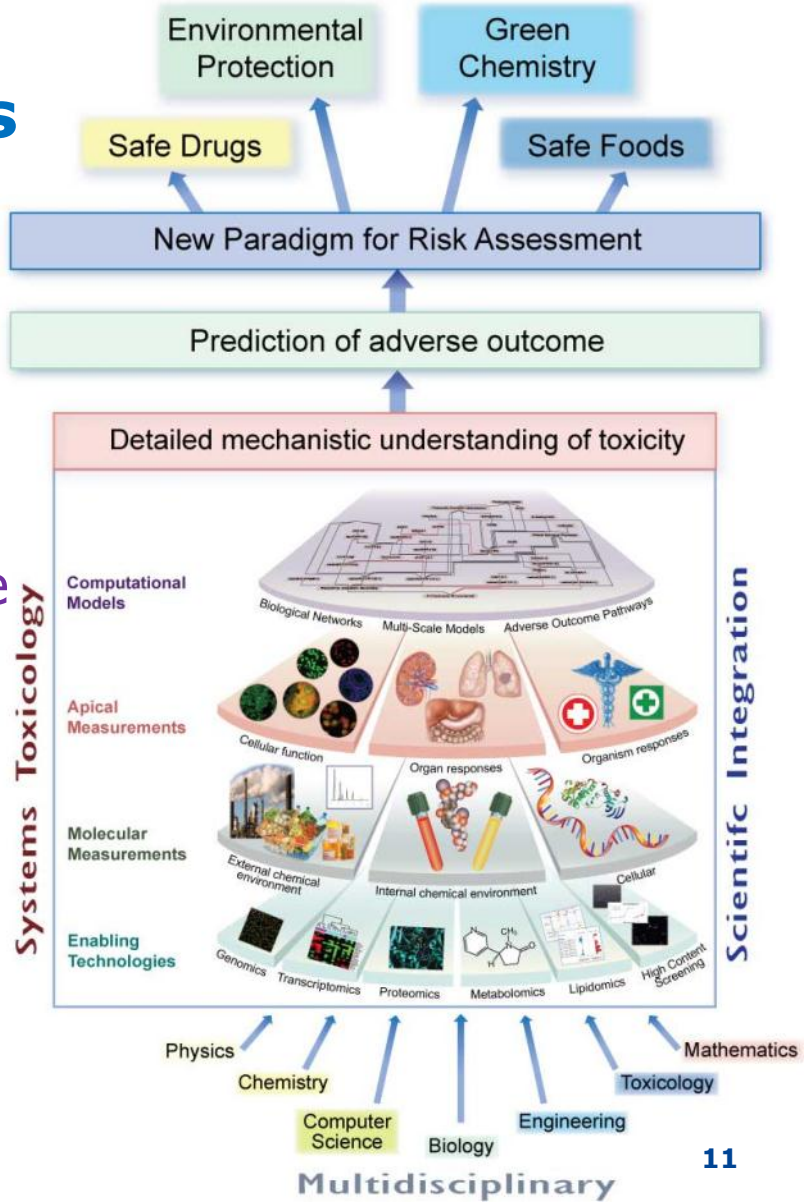
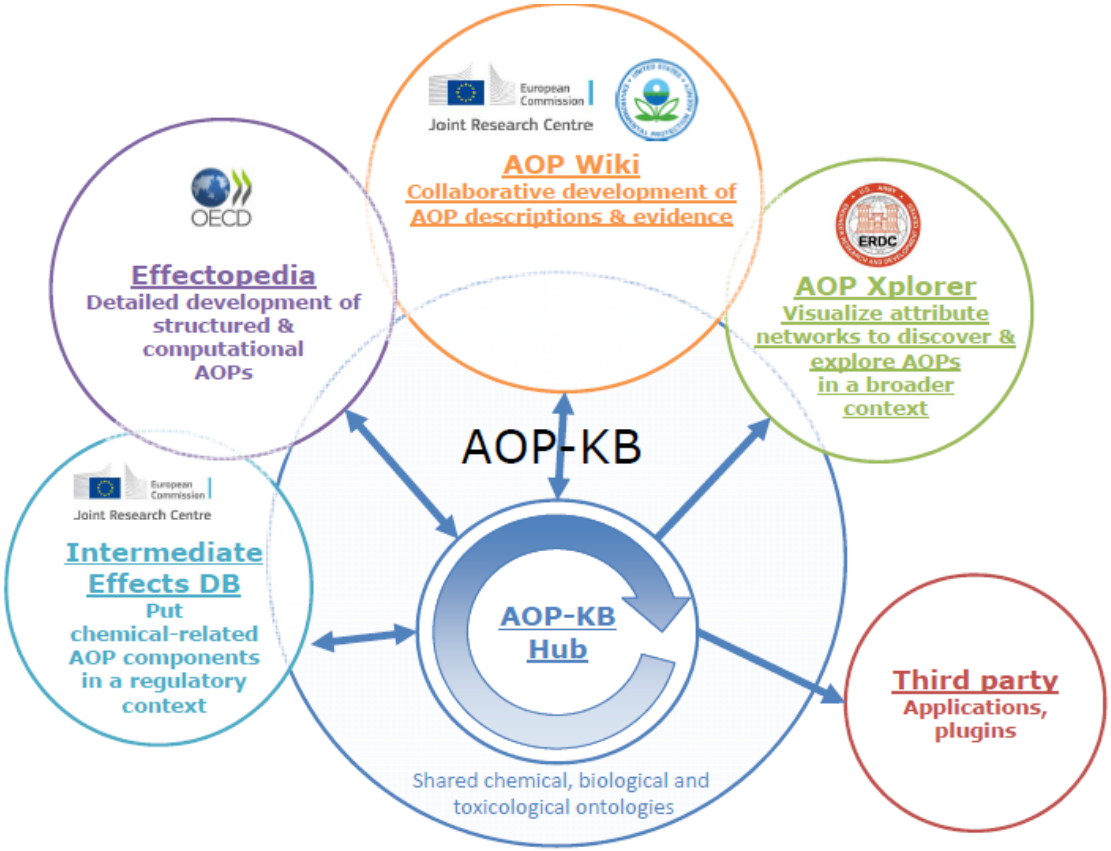


Figure from Sturla et al. (2014). Systems Toxicology: from basic research to risk assessment. Chemical Research in Toxicology

Structure the AOP information in collaboration with the rest of the world



Visit AOP Wiki (https://aopkb.org) to explore currently mapped AOPs, improve them or add new ones.

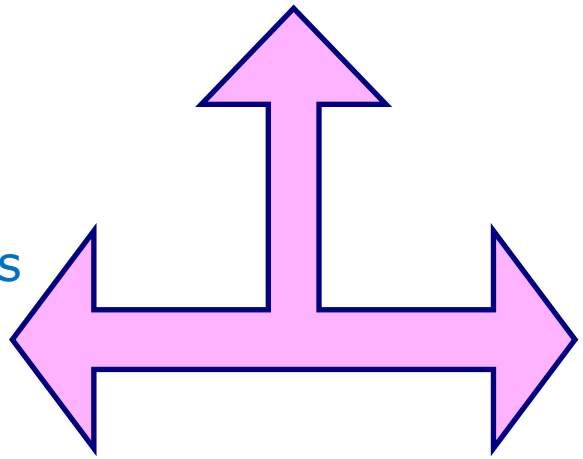
OECD
BETTER POLICIES FOR BETTER LIVES

From Adverse Outcome Pathways to Practical Applications

Integrated Approaches to Testing and Assessment (IATA)

- hazard identification
- priority setting

- classification & labelling
- risk assessment



Mechanistic information

- toxicokinetic pathways
- Adverse Outcome Pathways

Alternative Methods Toolbox

- *in chemico* assays
- *in vitro* assays
- *in silico* models
- chemical categories

IATA (Integrated Approaches to Testing and Assessment): a way to structure the information

- Generic guidance on the evaluation and application of an IATA for a certain health hazard
- Reporting template for IATA, thereby providing a harmonised framework for the documentation and evaluation of IATA
- Range of IATA solutions, covering different regulatory goals (hazard identification, classification, and potency assessment)

A GLOBAL THINKING - A LARGE HORIZON

Regulation 1290/2013
on participation in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)"

Regulation 1829/2003 on genetically modified food and feed

Regulation 726/2004
on authorisation and supervision of medicinal products for human and veterinary use

Proposal for a Regulation on veterinary medicinal products

Community Strategy on combined exposures 'Mixtures'

Community Strategy on Endocrine Disrupters

Regulation 440/2008
on test methods

Regulation 1223/2009
on cosmetics products

Proposal for a Regulation on Animal Health

Directive 91/414
on authorisation of plant protection active ingredient and products

Regulation 528/2012
on authorisation of biocidal active ingredients an products

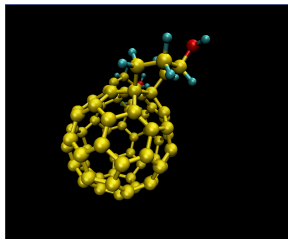
Regulation 1272/2008
on classification, labelling and packaging of chemical substances and mixtures (CLP)

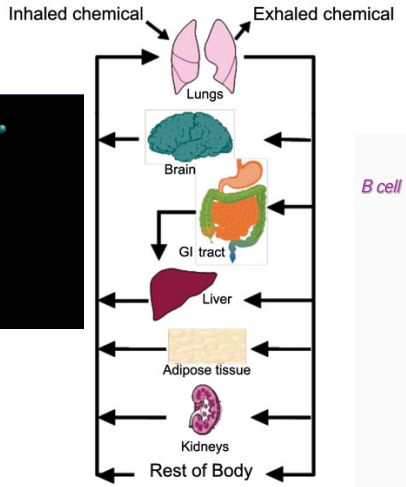
Regulation 1907/2006
on registration, evaluation, authorisation and restriction of chemical substances (REACH)

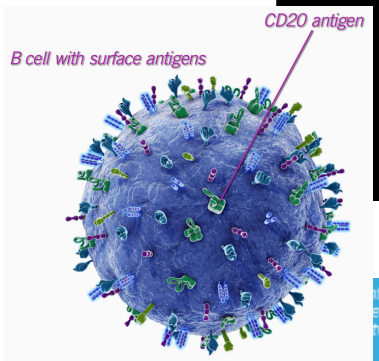
IATA an instrument for evolution

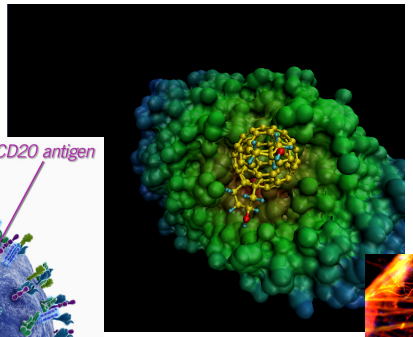
- The IATA is not validated, but indicates where methods are needed (relevance), and these methods might then be prioritized for validation, to guarantee robustness and reproducibility.

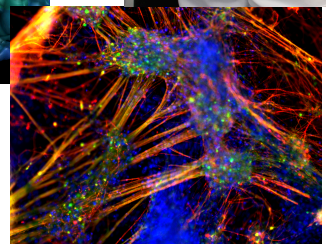
- The IATA is a structure encouraging flexibility providing space for development.

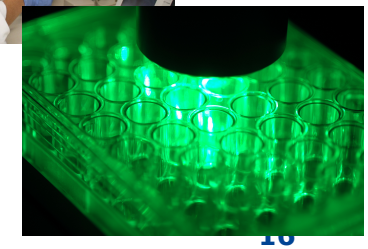












EURL ECVAM strategies

- ✓ Analysis of regulatory information needs
- ✓ Cross-sectorial scope
- ✓ Broad strategic aims
- ✓ Ambitious but pragmatic
- ✓ Solutions for regulatory acceptance
- ✓ International TGs and Guidance

https://eurl-ecvam.jrc.ec.europa.eu/eurl-ecvam-strategy-papers

EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

Seurat-1: towards replacement of *in vivo* repeated dose systemic toxicity testing

http://www.seurat-1.eu/

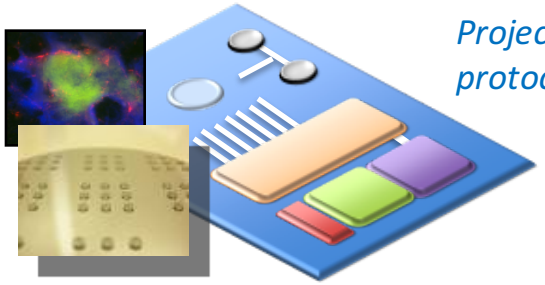
- *Cluster of seven collaborative projects*
- *50 million Euro investment*
- *Co-financed by EC and Cosmetics Europe*
- *Over 70 research partners*
- *16 countries plus EC*
- *6 year programme*

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.

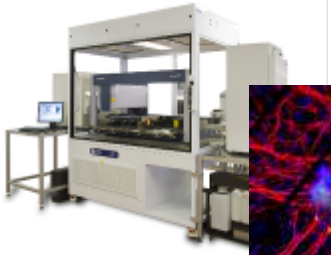
European Commission

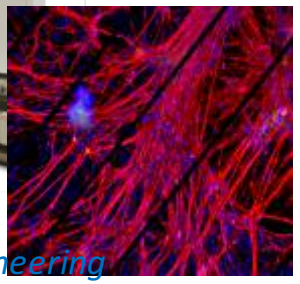
Cosmetics Europe

SEURAT-1 Alternative Methods Toolbox

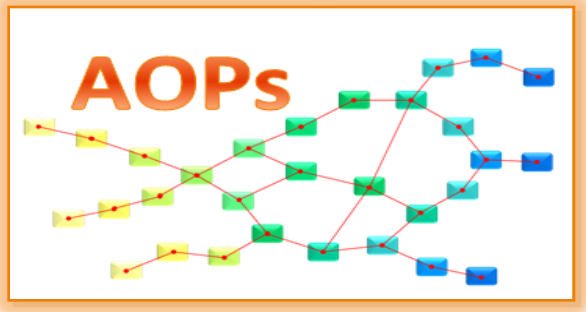


Project data and protocol warehouse

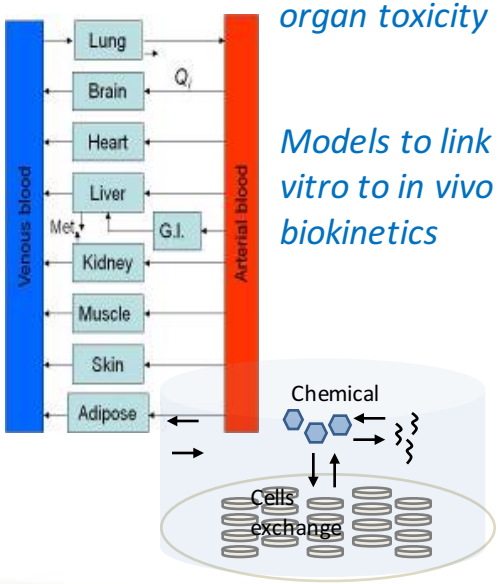




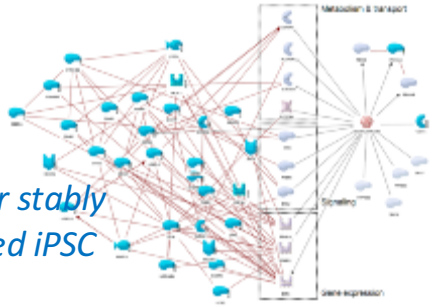
Bioreactors for engineering tissues



Multi-scale models of organ toxicity

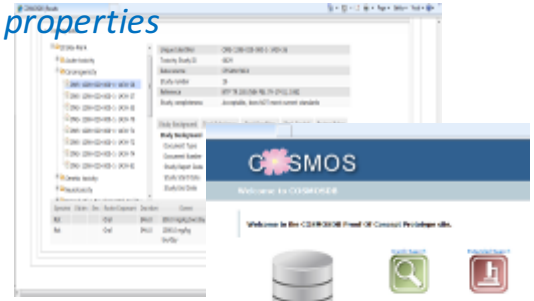


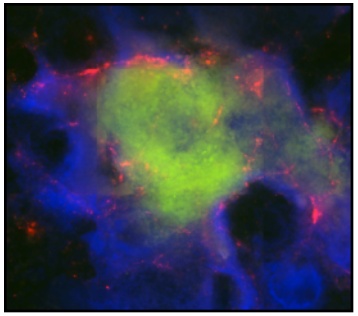
Models to link in vitro to in vivo biokinetics



Protocols for stably differentiated iPSC

Database on cosmetics ingredients and properties





Genetically engineered reporter-gene cell lines

Seurat-1Proof of Concept on three levels

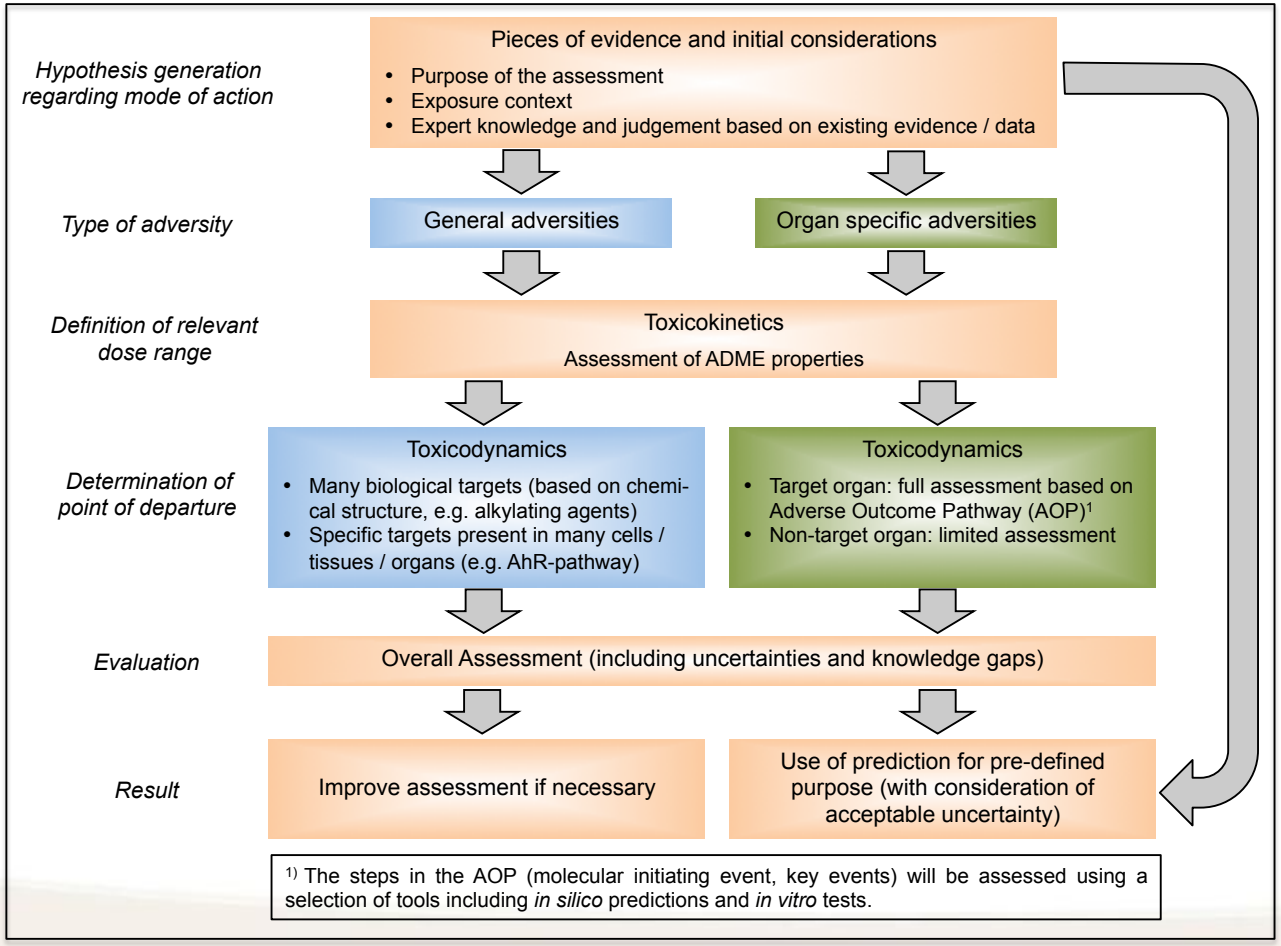
Level 3: Application of Predictive Systems to support regulatory Safety Assessment

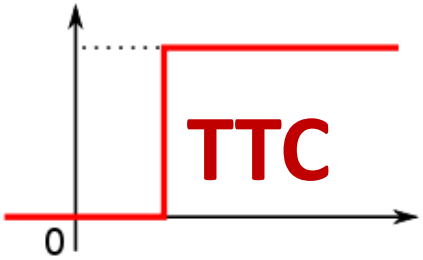
Level 2: Development of Integrated Testing Strategies to Predict Toxicity

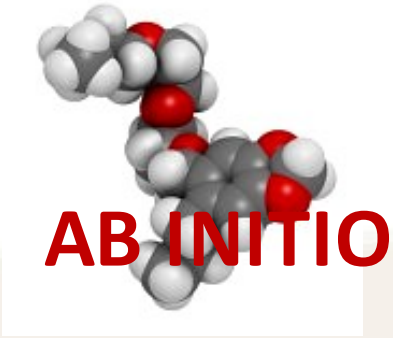
Level 1: Development of Adverse Outcome Pathway (AOP) constructs

Level 3: Safety Assessment

One conceptual framework - three case studies:







Four different scenarios

I. Chemical similarity of compounds that do not require metabolic transformation to exert a potential adverse human health effect

II. Chemical similarity involving metabolic transformation resulting in exposure to the same/similar proximal toxicant

III. Chemicals with general low or no toxicity

IV. Distinguishing chemicals in a structurally similar category with variable toxicities based on Mode of Action hypothesis

ehp ENVIRONMENTAL HEALTH PERSPECTIVES

REVIEW ADVANCE PUBLICATION

Environ Health Perspect; DOI:10.1289/ehp.1409342

Chemical Safety Assessment Using Read-Across: Assessing the Use of Novel Testing Methods to Strengthen the Evidence Base for Decision Making

Elisabet Berggren,[1] Patric Amcoff,[2] Romualdo Benigni,[3] Karen Blackburn,[4] Edward Carney,[5] Mark Cronin,[6] Hubert Deluyker,[7] Francoise Gautier,[8] Richard S. Judson,[9] Georges E. N. Kass,[7] Detlef Keller,[10] Derek Knight,[11] Werner Lilienblum,[12] Catherine Mahony,[13] Ivan Rusyn,[14] Terry Schultz,[15] Michael Schwarz,[16] Gerrit Schüürmann,[17] Andrew White,[18] Julien Burton,[1] Alfonso M. Lostia,[1] Sharon Munn,[1] and Andrew Worth[1]

SEURAT-1

Contents lists available at ScienceDirect

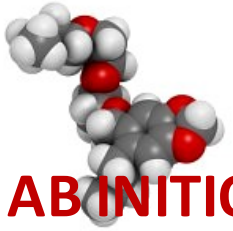
Regulatory Toxicology and Pharmacology

Regulatory Toxicology and Pharmacology 72 (2015) 586–601

ELSEVIER

A strategy for structuring and reporting a read-across prediction of toxicity ☆

T.W. Schultz [a], P. Amcoff [b], E. Berggren [c], F. Gautier [d], M. Klaric [b], D.J. Knight [e], C. Mahony [f], M. Schwarz [g], A. White [h], M.T.D. Cronin [i,*]

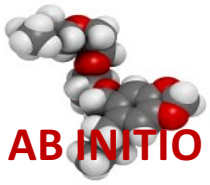


AB INITIO

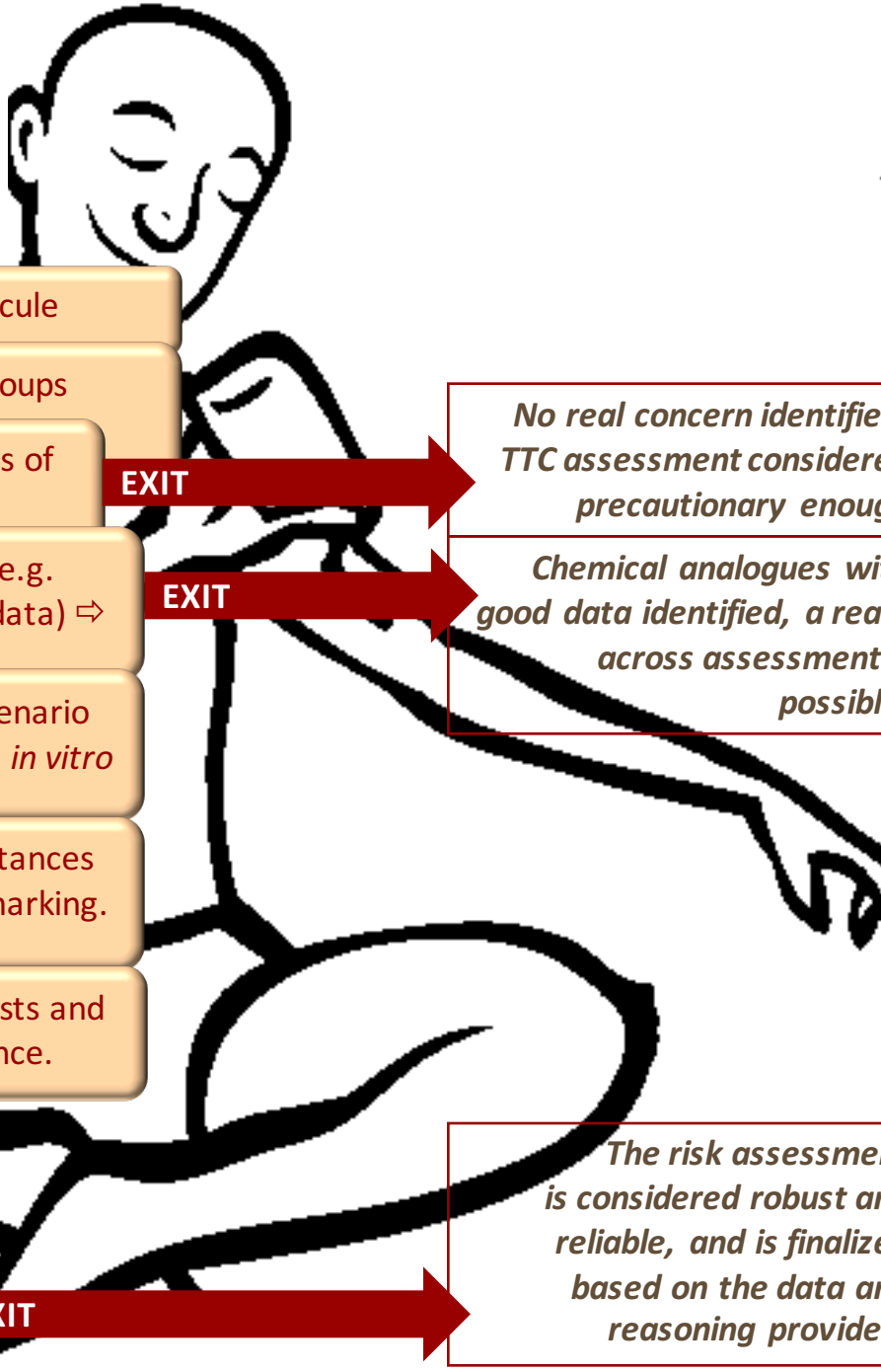
Level 3: The Ab initio case study

Our case study:

Can we safely use 12.5% Piperonyl butoxide (PBO) in a body lotion applied twice a day (corresponding to 144.797mg/kg/day)?



Level 3: Ab initio workflow



1. Set up relevant exposure scenario
2. Collect phys chem properties of the molecule
3. Identify molecular structure and active groups
4. Identify molecular structures and active groups of predicted/possible metabolites

EXIT → *No real concern identifie… TTC assessment considere… precautionary enou…*

NEW HYPOTHESIS

5. Evaluation of 1-4 together and Tier 1 data (e.g. exisiting profiling data like omics and ToxCast data) ⇨ hypothesis

EXIT → *Chemical analogues wi… good data identified, a rea… across assessment… possibl…*

6. Toxicokinetic modelling based on exposure scenario ⇨ estimate internal dose and relevant dose for *in vitro* testing
7. Predict corresponding concentrations for substances with known effects (in target organ) for benchmarking.
8. Evaluate which alternative methods (in vitro tests and in silico models) could provide useful evidence.

MORE EVIDENCE NEEDED

9. Perform testing/modelling to confirm/dismiss the hypothesis.
10. Collect and evaluate all data.
11. Final risk assessment or summary on insufficient information.

EXIT → *The risk assessme… is considered robust a… reliable, and is finalize… based on the data a… reasoning provide…*

Final Reporting

Everyone is welcome

Register at:
http://www.seurat-1.eu/


Arch Toxicol
DOI 10.1007/s00204-014-1421-5 November 2014

RESEARCH ARTICLE

SEURAT: Safety Evaluation Ultimately Replacing Animal Testing—Recommendations for future research in the field of predictive toxicology

George Daston · Derek J. Knight · Michael Schwarz · Tilman Gocht · Russell S. Thomas · Catherine Mahony · Maurice Whelan

Horizon 2020 project: EUToxRisk21
Starting this autumn will continue what SEURAT-1 started.

Topical Scientific Workshop - New Approach Methodologies in Regulatory Science

19-20 April 2016 | Helsinki, Finland

Topical scientific workshops of the European Chemicals Agency (ECHA) aim to foster discussion among academia, regulators, industry and other stakeholders on the possible regulatory impacts of the latest scientific developments. An anticipated outcome of these workshops is the emergence of new or improved approaches which may be applied to the implementation of the REACH, CLP and biocides regulations.

Aim of the workshop

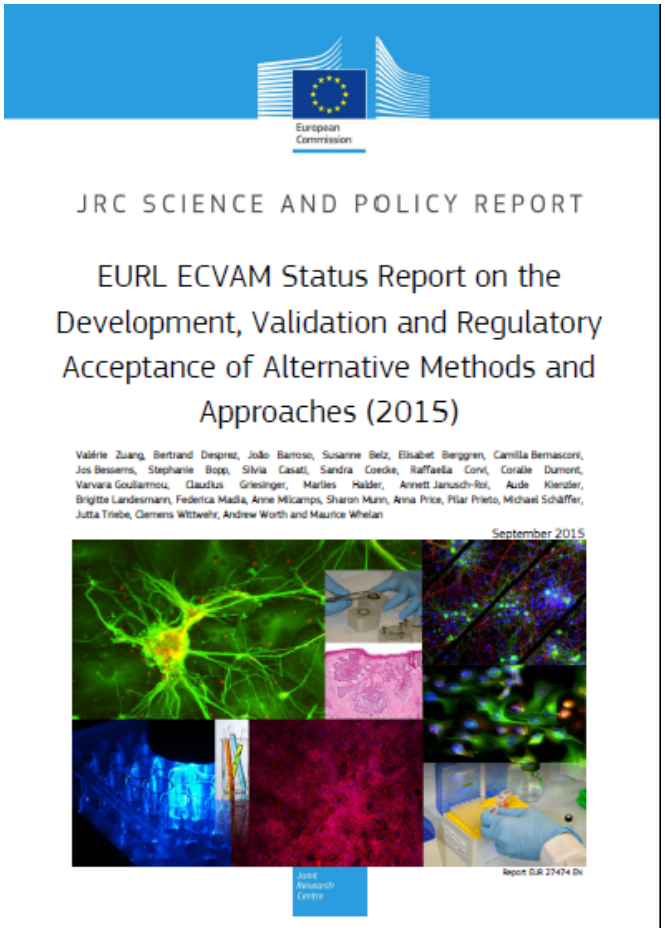
The Topical Scientific Workshop on New Approach Methodologies in Regulatory Science will explore the potential regulatory benefits arising from fundamental change in scientific thinking. Complex toxicological apical endpoints cannot be predicted by a single non-standard test. Instead, it is necessary to combine multiple lines of evidence (including '-omics' and high-throughput screening methods) to predict the hazardous property with tools to facilitate th

Two motivating drivers for the workshop are:

- A better understanding of the underlying biology behind how chemicals cause adverse effects to human health; and
- New tools and techniques that provide a huge amount of data to be used in solving regulatory issues.

The workshop draws inspiration from the EU research programme SEURAT-1 and the US Tox21 initiative, but also takes from the scientific field.

The yearly update on alternatives: The EURL ECVAM Status Report



Just published & available at
http://publications.jrc.ec.europa.eu/repository/handle/JRC97811

Joint Research Centre

Thanks for your attention!

elisabet.berggren@ec.europa.eu

THANK YOU FOR THE ATTENTION