Development and Validation of Alternative Methods

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Alternative Methods and ECVAM
The Institute for Health and Consumer Protection (IHCP)
Science for a healthier life

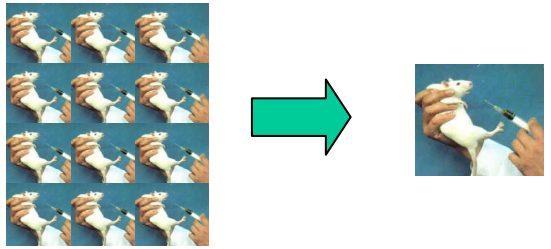
OUTLINE

- History
- Validation principles
- Successes and next challenges
- ECVAM Role

Two British scientists, Bill Russell and Rex Burch introduced the "3Rs" as a framework for considering the humane use of animals.

Refine

Reduce



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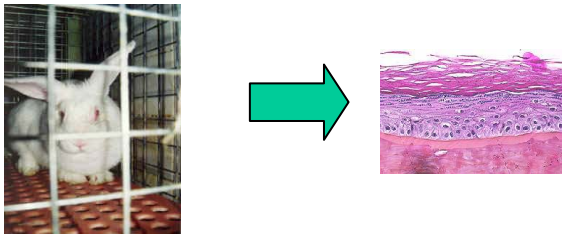

86/609/EEC

Russell, W. M. S. and Burch, R. L. 1959. The principles of humane experimental technique Special Edition, Universities Federation for Animal Welfare, Potters Bar, England

ECVAM

- Founded in 1991 to promote 3R methods primarily by confirming their scientific validity
- From 1991 to 2009 ECVAM was hosted within one JRC scientific Unit of the former Environment Institute (1991-1998) and of the Institute for Health and Consumer Protection (1998-2008)
- Since 2009 ECVAM is a Centre hosted by the Institute for Health and Consumer Protection and is served by mainly two scientific Units
- ECVAM has its own scientific advisory committee (ESAC)

ECVAM

- So far developed/optimised and/or validated 34 methods alternative to animal testing according to generally accepted validation principles
- Most methods have similar toxicological endpoints, i.e. skin and eye irritation; many methods are not replacement methods
- Maintains a database on alternative test methods (DB-ALM)
- Promotes method development through own research as well as through participation in RTD projects that will yield new methods
- Contributes to the regulatory acceptance of alternative methods

ECVAM's MISSION STATEMENT

To support the EU policies in the field of Consumer protection, Environmental protection and Animal protection

by validating alternative methods for safety testing that implement the 3Rs and provide the same or a better basis for risk assessment and risk management as current methods

and by promoting their development, their application in industry and their acceptance by regulators.

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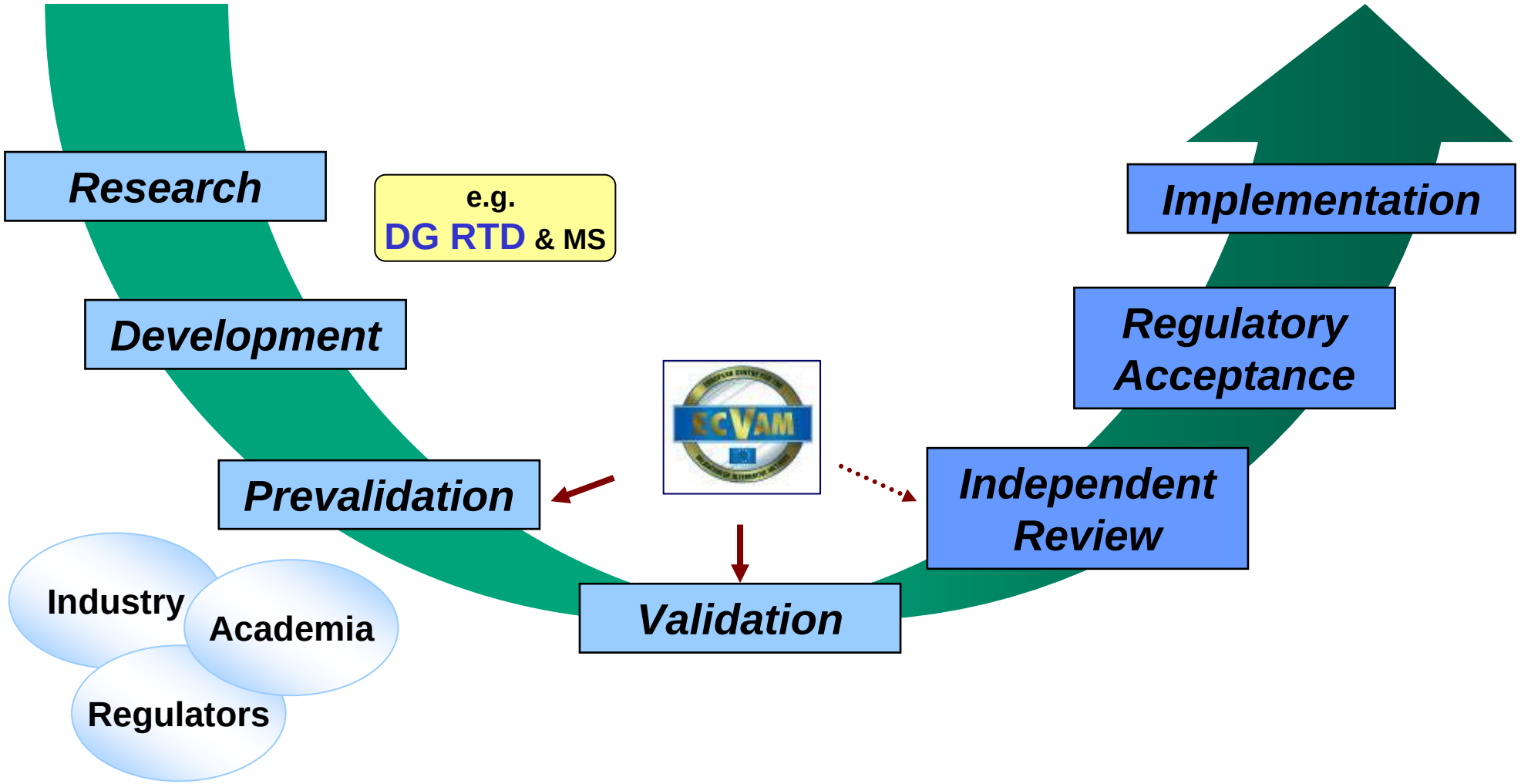
Research
e.g.
DG RTD & MS
Development
Prevalidation
Validation
Independent Review
Regulatory Acceptance
Implementation
Industry
Academia
Regulators

Information requirements that validation studies endeavour to satisfy

Test method definition	*Module 1 – Test definition:* ***test system, SOP, prediction model, development, possible use, limitations, etc.***
Reliability *Concordance/ Discordance*	*Module 2 – Within laboratory reproducibility:* ***sufficiently standardized to give reproducible results in one lab ?***
	Module 3 – Transferability: ***transferable, and yes, how readily?***
	Module 4 – Between laboratory reproducibility: ***how reproducible between labs?***
(Predictive) Relevance *Accuracy*	*Module 5 – Predictive capacity:* ***Specificity, Sensitivity, Overall Accuracy***
	Module 6 – Applicability domain/Limitations: ***Which xenobiotics can NOT be tested?***
Performance criteria	*Module 7 – Performance Standards:* ***Performance Acceptance Criteria for new tests that are sufficiently similar to the validated one***

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ECVAM activities & involvement, Per endpoint, 2009

	Development	Prevalidation	Validation	Reg. acceptance	Post- reg. -acceptance
Skin Corrosion	✓	✓	✓	✓	✓
Acute Phototoxicity	✓	✓	✓	✓	
Skin Absorption / Penetration	✓	✓	✓	✓	
Skin Irritation	✓	✓	✓	✓	✓
Eye Irritation	✓	✓	✓*	✓*	
Acute Toxicity	✓	✓	✓*		✓*
Genotoxicity / Mutagenicity	✓	✓	✓*	✓*	✓*
Skin Sensitisation	✓	✓	✓*	✓*	✓*
Reproductive & Developmental	✓	✓	✓*	✓*	
Toxicokinetics / Metabolism	✓	✓	✓*		
Carcinogenicity	✓	✓*	✓*		
Subacute & Subchronic Toxicity	✓				
Biologicals, vaccines	✓	✓	✓	✓	✓

* Reduction / refinement alternatives

Human health effects

Skin Corrosion

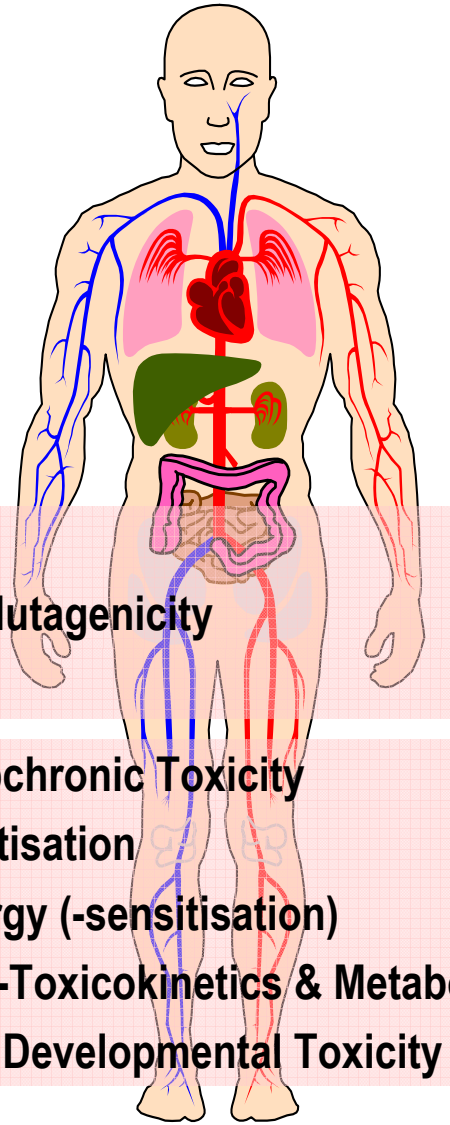
Acute Phototoxicity

Skin Absorption / Penetration

Skin Irritation

Photogenotoxicity

Eye Irritation



Acute Toxicity

Genotoxicity / Mutagenicity

Subacute & Subchronic Toxicity

Skin Sensitisation

Photo-allergy (-sensitisation)

Carcinogenicity-Toxicokinetics & Metabolism

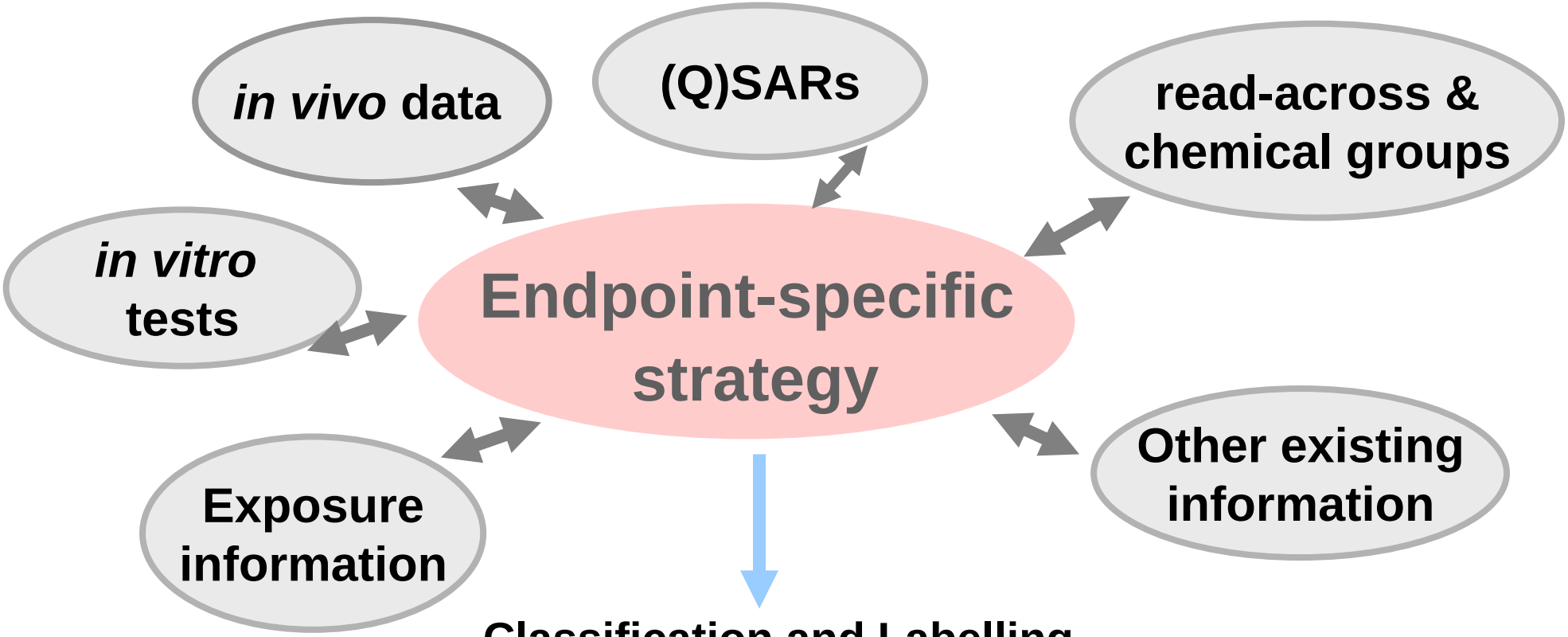
Reproductive & Developmental Toxicity

Biggest challenge

Systemic Toxicity - Systems Biology

- Metabolism
- Multiple modes of action
- Dose/response
- One to one replacement not possible
- Battery of test methods
- Tiered testing strategies
- Combination of disciplines (*in vitro/in silico/in vivo/PBPK models*)
- **Integrated testing strategies**

Integrated Testing Strategies

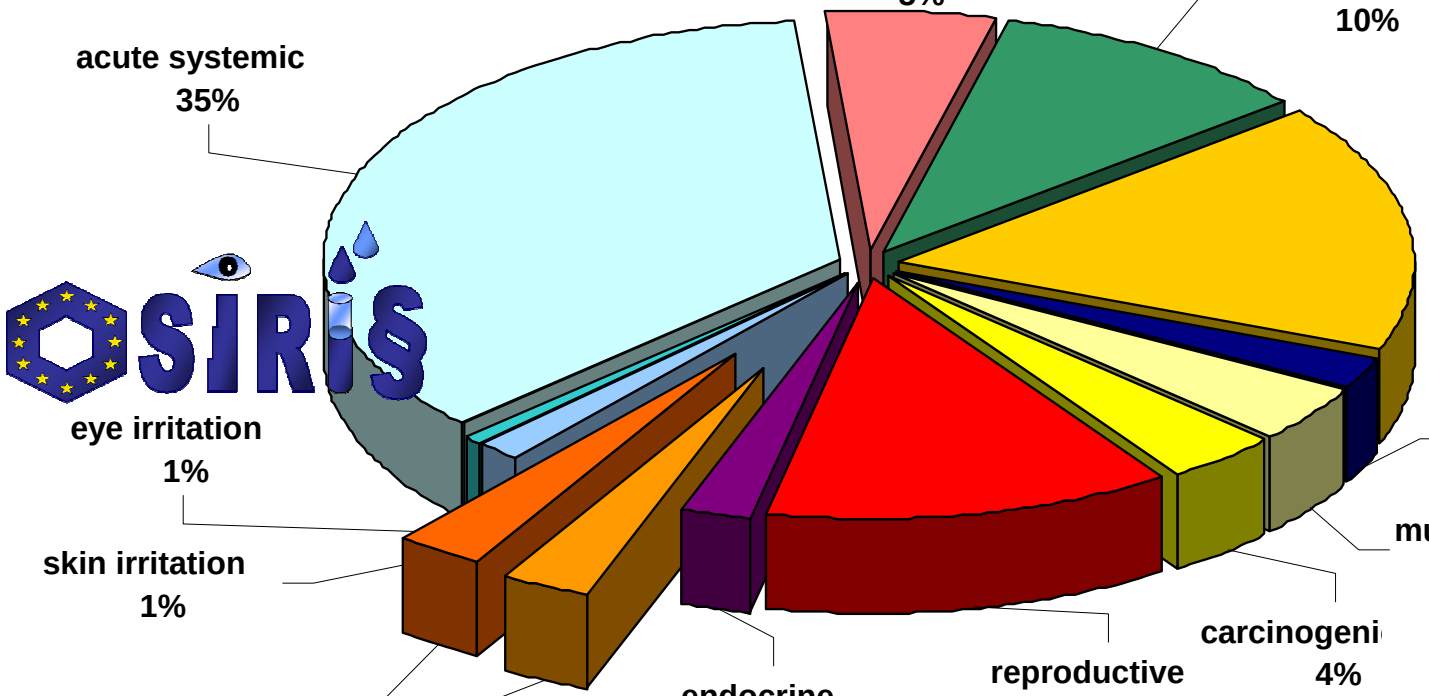


Classification and Labelling,
Risk Assessment of Chemicals and Persistent Bioaccumulative Toxic Chemicals

Risk Management Measures

New/emerging technologies

- Human cell-based metabolically competent liver cells
- Human stem cell-derived neurons/micro electrode arrays
- 3D in vitro tissue models
- Automation of in vitro methods (HTS/HCS)
- Development of computational methodology (in silico, QSAR)
- 'Omics', genomics, proteomics, metabonomics



SIXTH FRAMEWORK PROGRAMME

SENS-IT-IV

PULMO-NET

PREDICTOMICS

PREDICT-IV

Vitrocellomics

carcinoGENOMICS
a Project of the European Union

TOXDROP

RePrOTect

ESNATS

inVitroHeart

SEVENTH FRAMEWORK PROGRAMME

EC Call for proposals on Alternative Testing Strategies in field of repeated dose systemic toxicity– 7th Framework programme

- COLIPA matched funding to EC (Eur 25 + 25 million)
- Open call – 30 July 2009 to 3 Feb 2010

Validation of Integrated Testing Strategies?

- Validate ITS or Building blocks of ITS or both?
- Building blocks (reliability (modules 1-4) sufficient?)
- Predictive capacity – validate against what?
- Validation should be 'fit for purpose'
- Need case studies

Overcoming Barriers to Validation of Non-animal Partial replacement Methods/Integrated testing Strategies: The Report of an EPAA-ECVAM Workshop. ATLA, 37,437-444,2009

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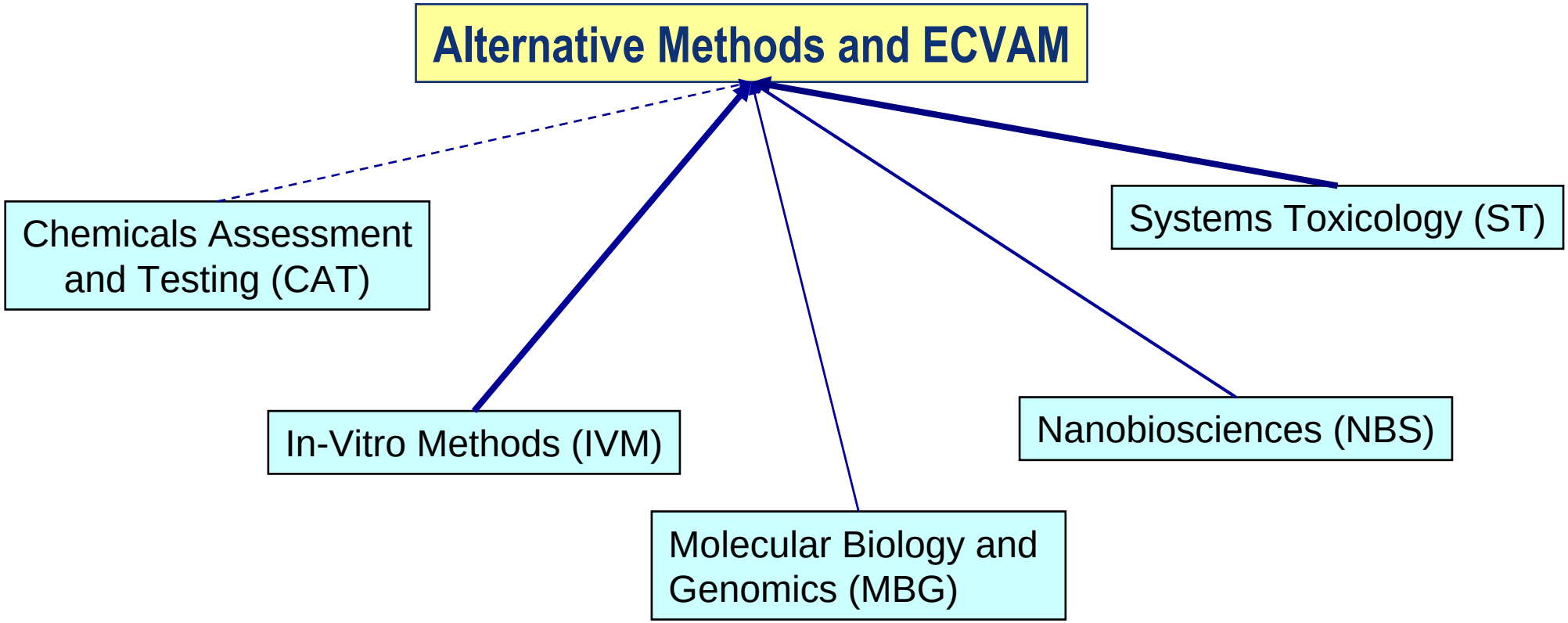
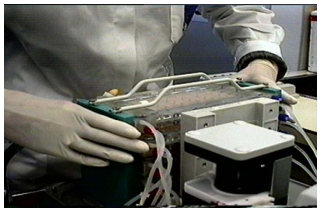
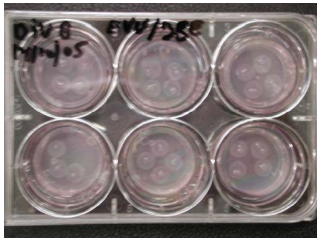
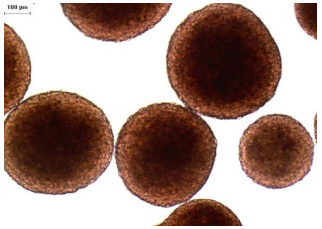
JRC-IHCP Units Supporting ECVAM

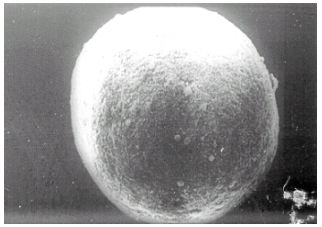


ECVAM has now full access to the broad range of competencies available across the Institute.







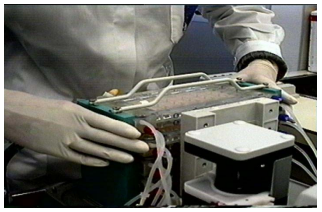


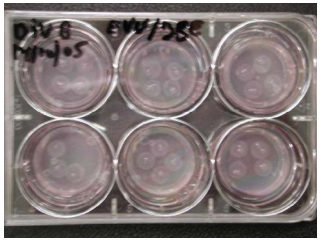
The relevant competencies include:

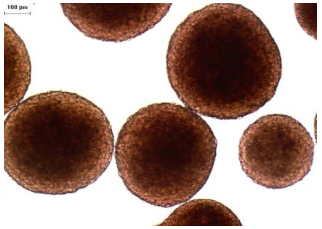
- **at cellular level: in vitro methods, working with many different (human) cell systems and their automation towards high throughput;**
- **at sub-cellular level: "omics" (metabonomics, genomics);**
- **at molecular or chemical level: computational chemistry including QSAR.**

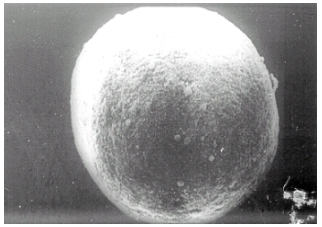
PBPK and modeling expertise to help connect the cellular and sub-cellular levels with the organ or organism level.

Wealth of experience on validation of alternative methods







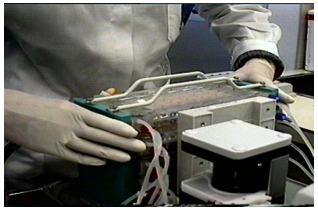
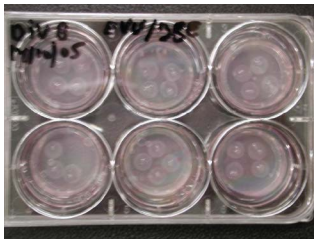
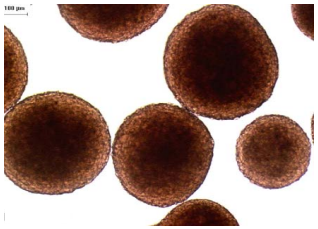
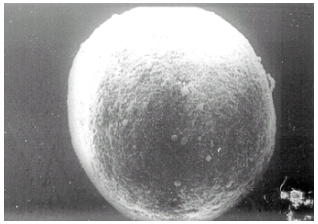


Validating alternative methods that provide the same or better basis for risk assessment as current methods

INNOVATION: contribute to methods/testing strategies that reduce reliance on in vivo animal studies even for complex endpoints

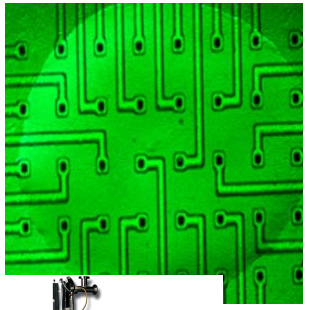
VALIDATION: continue to manage and coordinate scientific validation of submitted methods, assessing robustness, reliability, predictive capacity of methods and regulatory relevance, promoting regulatory acceptance

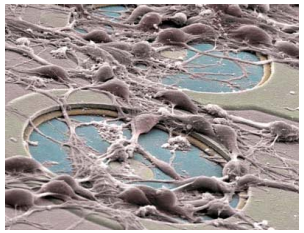
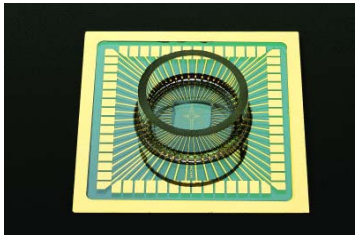
COMMUNICATION: engage with regulators/risk assessors, test developers, test users/risk assessors, promote dialogue/cross talk through workshops, promote uptake of methods though dissemination

Concluding remarks

- **Integrated testing strategies required to address complex endpoints**
- **Emerging technologies give opportunity to make a gear change in progress**
- **A major challenge lies in the integration of the data and its interpretation in relation to specific regulatory questions**
- **Risk assessors need to engage in dialogue to give a steer to increase chance of relevant outcomes (both development and validation aspects)**

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EUROPEAN COMMISSION

ECVAM

ihcp
Institute for Health and Consumer Protection

Alternative Methods to Animal Testing:
Improving the Scientific Basis for the Protection of Human Health and the Environment while Reducing the Need for Animal Testing

for more information visit
http://ecvam.jrc.ec.europa.eu/

European Centre for the Validation of Alternative Methods

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