REACH and beyond - but not beyond reach!

Claudius Griesinger, Thomas Hartung, ECVAM team.

Key area leader

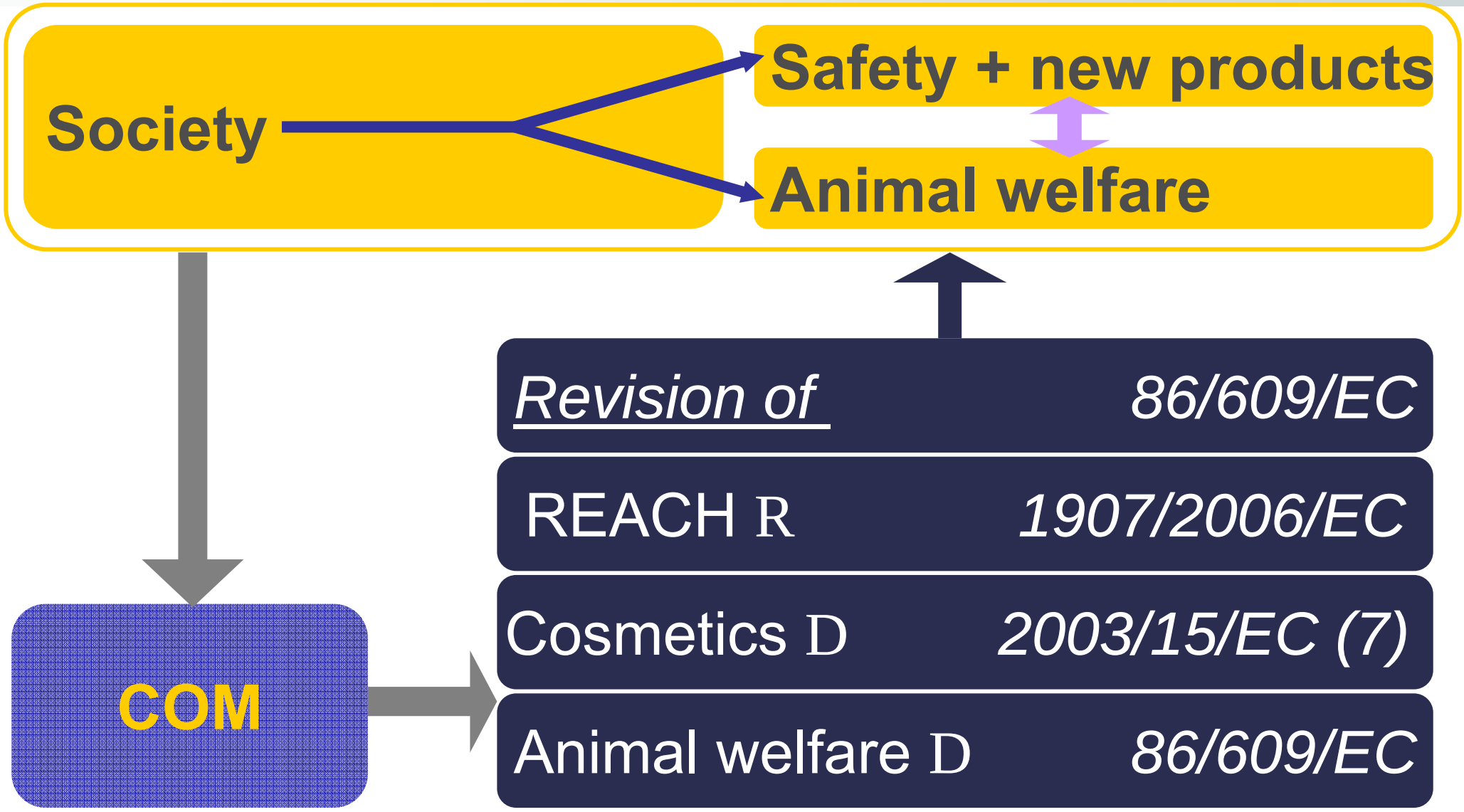
- *Evidence-Based Toxicology (EBT)*
- *CORRELATE ('Commission Reference Laboratory for Alternative Test Evaluation')*

OVERVIEW

Driving forces:

translating societal expectations into legislation

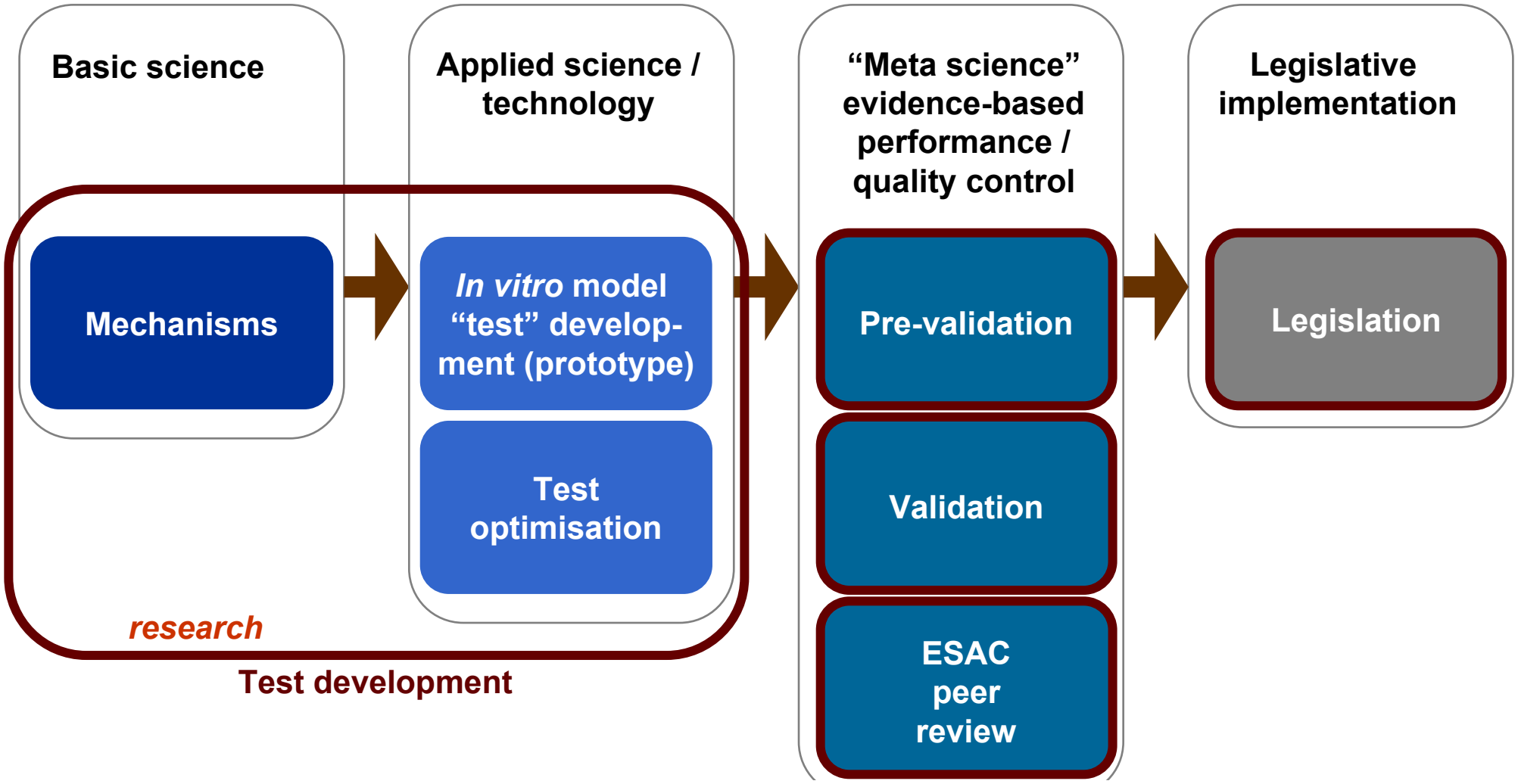
The driving force: societal expectations of sustainability



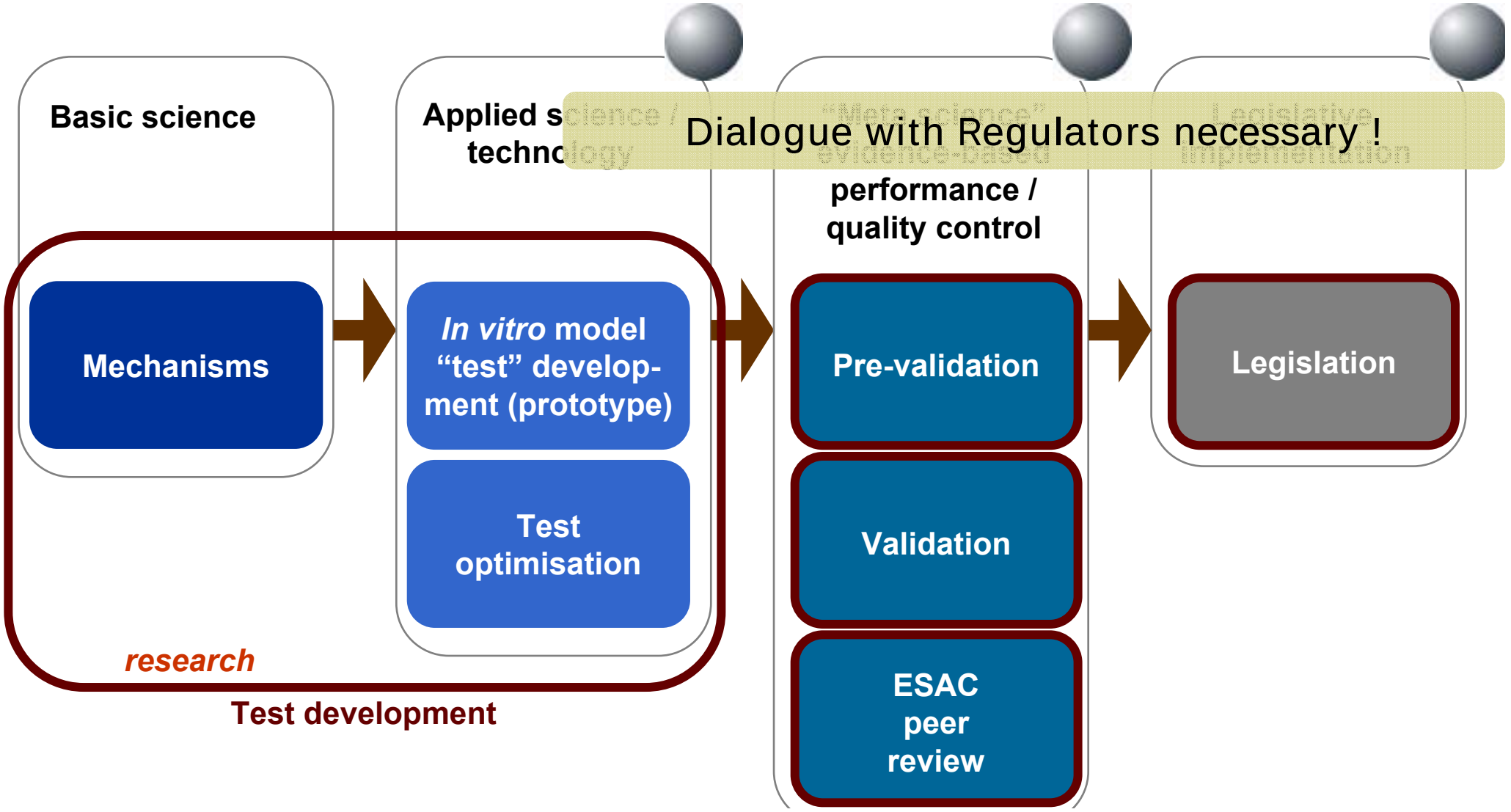
ESAC statements. *chemicals*

ESAC Statement	Date	67/548/EEC	OECD
• 3T3 NRU phototoxicity test	**1997**	2000	2002
• EPISKIN™ skin corrosivity test	**1998**	2000	2002
• Rat TER skin corrosivity test	**1998**	2000	2002
• 3T3 NRU phototoxicity test to UV filter chemicals	**2000**		
• Local Lymph Node assay for skin sensitisation	**2000**		2002
• EpiDerm™ skin corrosivity test	**2000**	2000	2002
• CORROSITEX ® skin corrosivity test	**2000**		2006
• Embryonic stem cell test for embryotoxicity	**2002**		
• Whole-embryo culture test for embryotoxicity	**2002**		
• Micromass test for embryotoxicity	**2002**		
• Micronucleus test, alternative to in vitro chromosome abberation	**2006**		
• SkinEthic skin corrosivity test	**2006**		
• BCOP / ICE test for identifying severe eye irritants	**2007**		
• rLLNA (reduced local lymph node assay – skin sensitisation)	**2007**		
• EPISKIN (MTT.IL1a) + EpiDerm (MTT) – skin irritation (full & partial replacement)	**2007**		

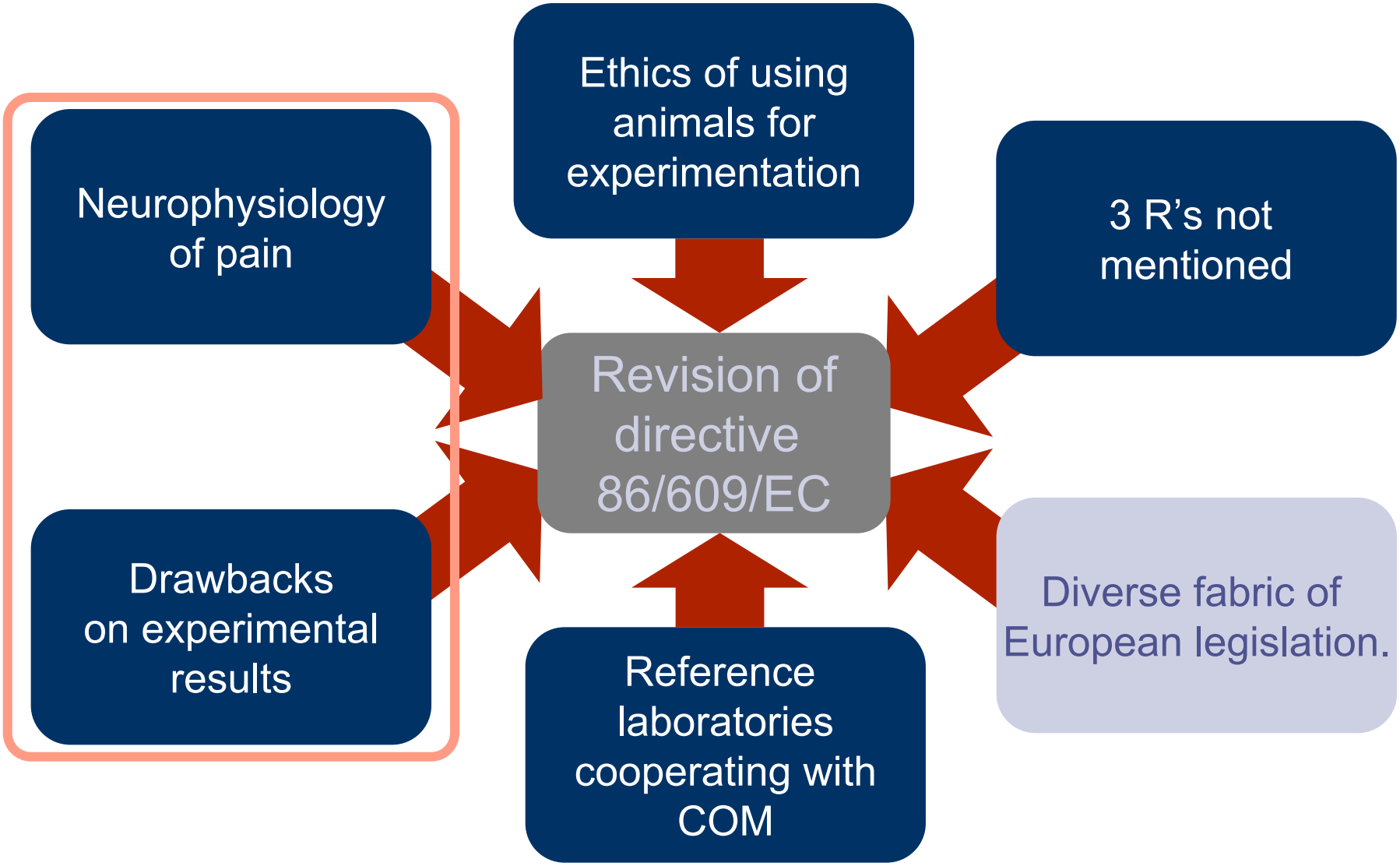
Ante / pre / validation / post



Ante / pre / validation / post



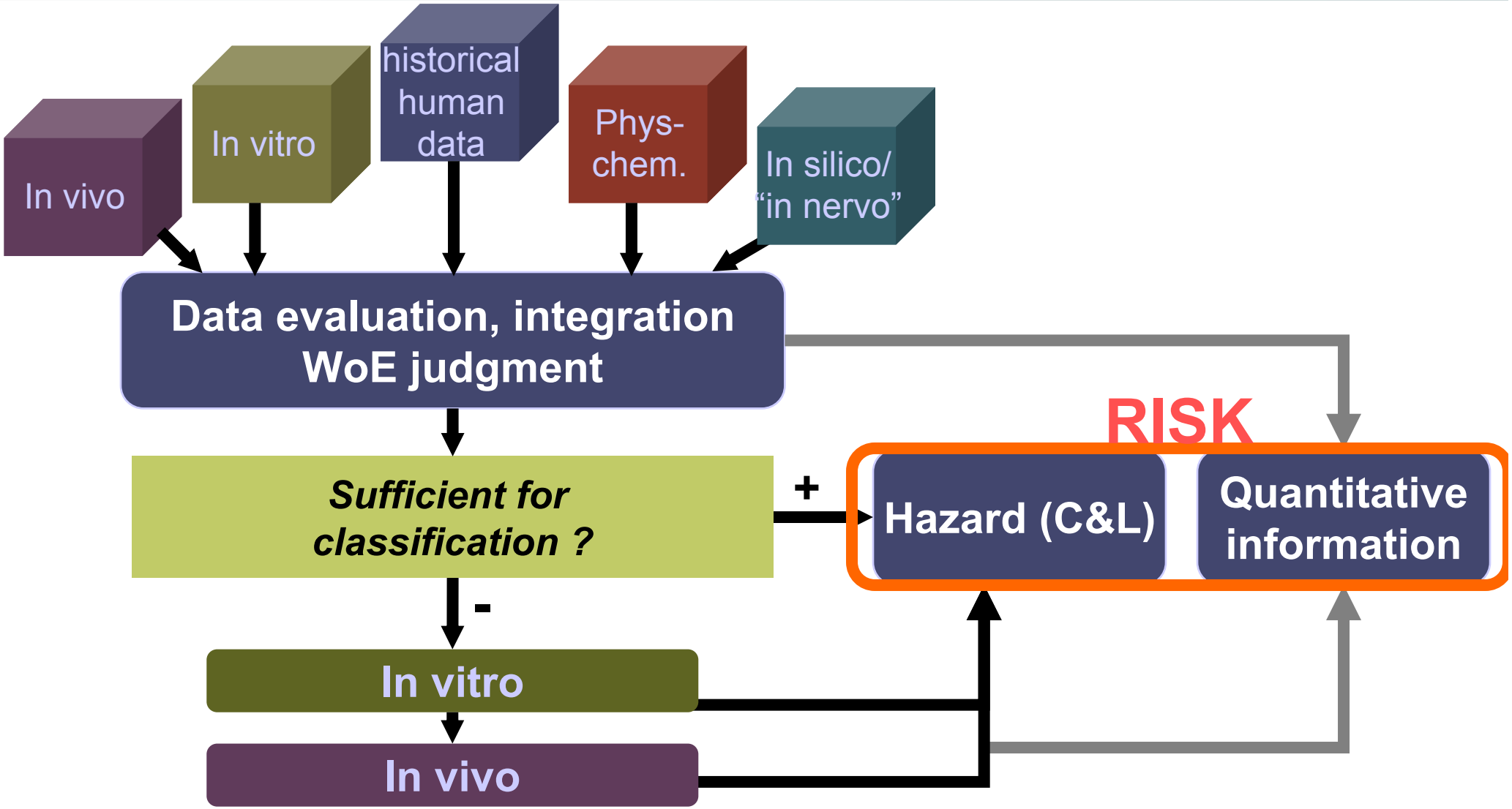
Revision of 86/609/EC



OVERVIEW

Key legislations:
REACH & Article XI

General (simplified!) testing strategy (REACH)



REACH and alternative methods

Whereas 1

Article 1

Article 13

Article 25

Annex XI

REACH and in vitro – Whereas 1

Whereas 1

The purpose of this Regulation is to ensure a high level of protection of human health and the environment,
as well as the free movement of substances, on their own, in preparations and in articles while enhancing competitiveness and innovation. This Regulation should also promote the **development of alternative methods for the assessment of hazards of substances.**

REACH and in vitro – Article 1

Article 1

Aim and Scope

The purpose of this Regulation is to ensure a high level of protection of human health and the environment, **including the promotion of alternative methods for assessment of hazards of substances**, as well as the free circulation of substances on the internal market while enhancing competitiveness and innovation.

REACH and in vitro – Article 13

Article 13

General requirements for generation of information on i. p. of substances

(3)
To generate information, conduct in accordance with „...**test methods laid down in a Commission regulation** or other international test methods recognised by the Commission or the Agency as being appropriate."

„....information ... may be generated in accordance with other test methods provided that the conditions set out in Annex XI are met."

REACH and in vitro – Article 25

Article 25

Objectives and General Rules

In order to avoid animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken **only as a last resort.** It is also necessary to take measures limiting duplication of other tests.

REACH and alternative methods

Whereas 1	*Development*	
Article 1	*Promote their use in hazard testing*	
Article 13	*Not only 'canonized' methods -> val. AM's*	Annex XI
Article 25	*Their use indirectly encouraged*	

REACH – Annex XI

Annex XI

General rules for adaptation of the standard testing regime set out in Annexes VII to X

1. Standard (often Animal) **Testing does not appear scientifically necessary**

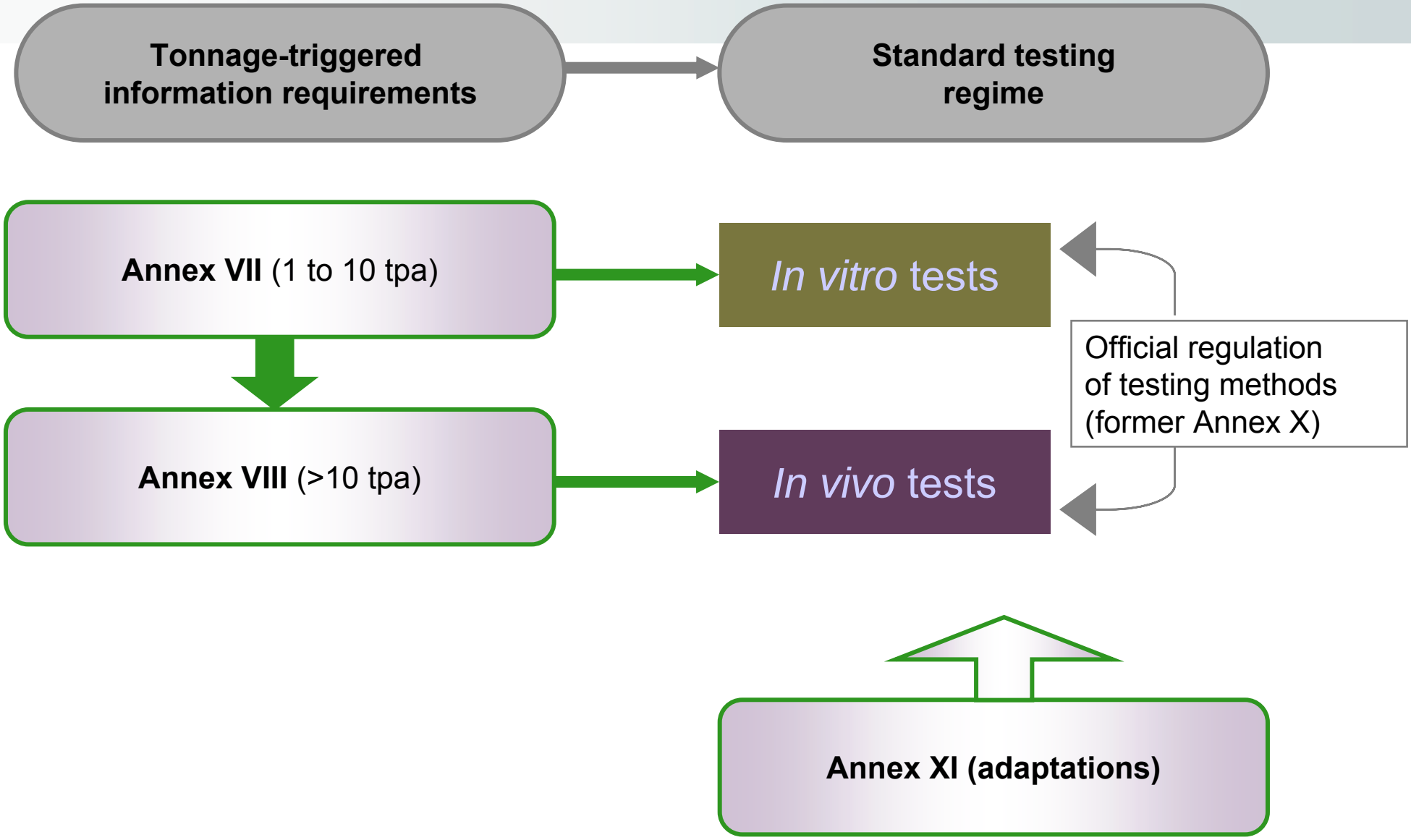
1.1 Use of existing data

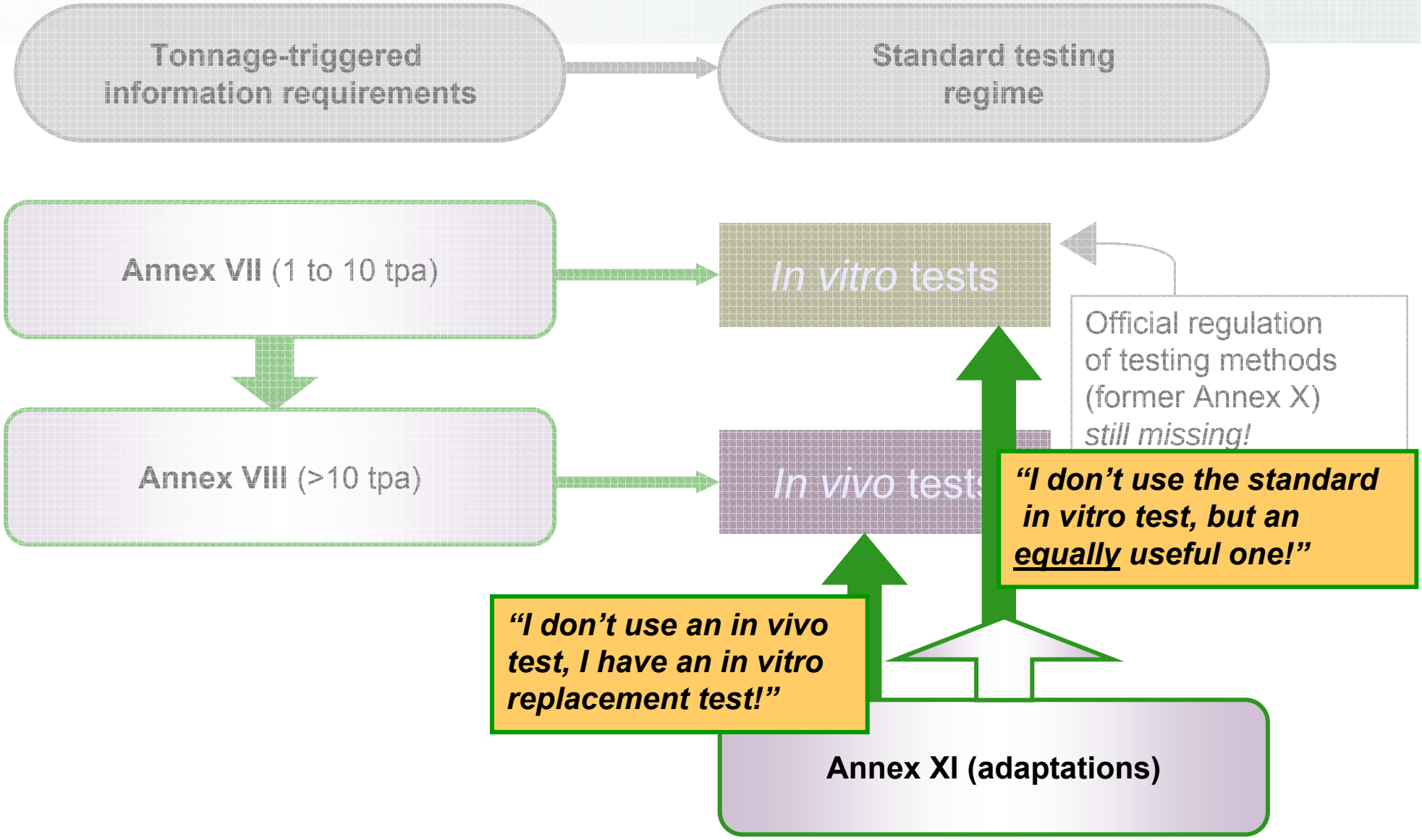
1.2 Weight of evidence

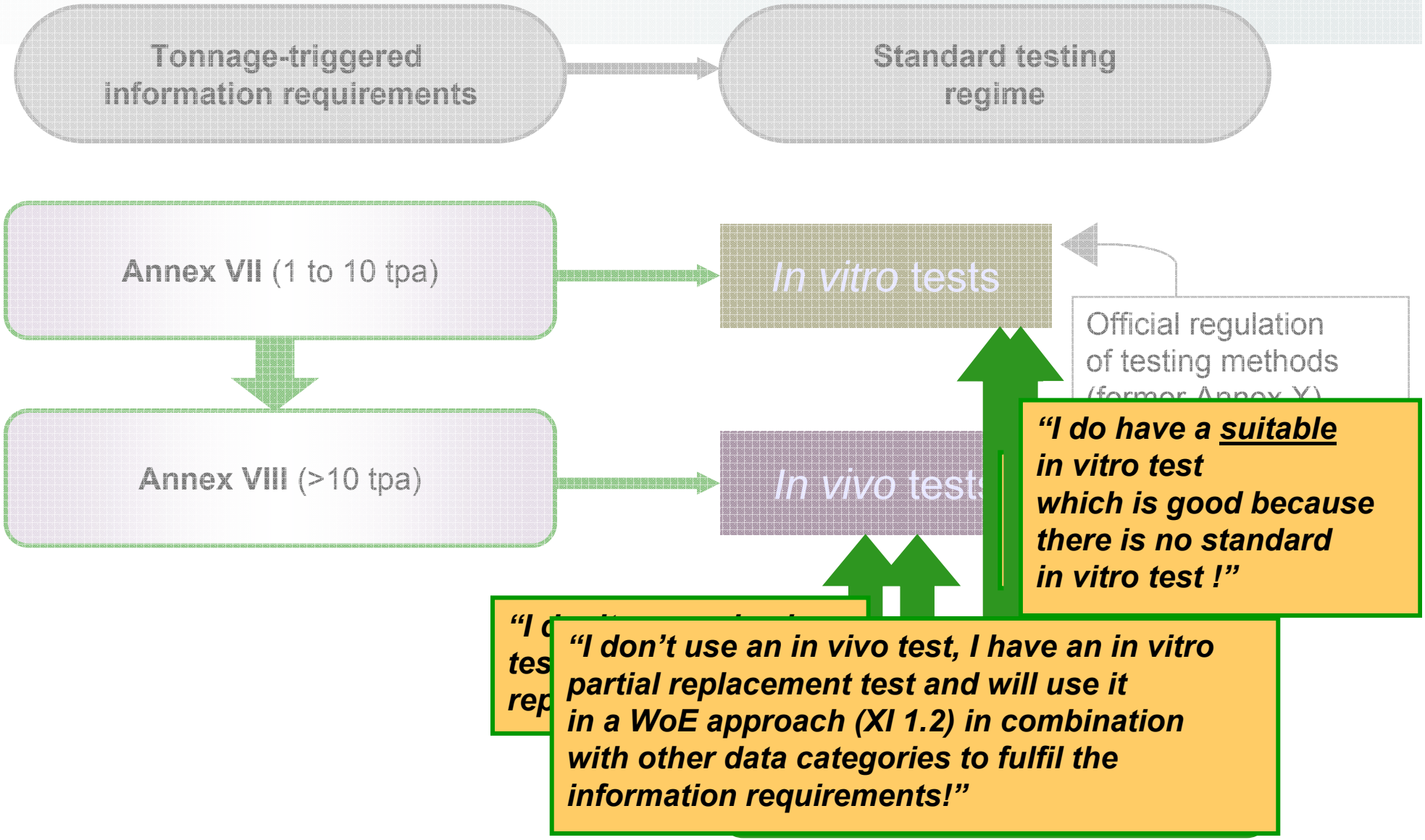
1.3 Qualitative or quantitative structure-activity relationships

1.4 In vitro methods

1.5 Grouping of substances and read-across approach


Tonnage-triggered information requirements
Standard testing regime
Annex VII (1 to 10 tpa)
Annex VIII (>10 tpa)
In vitro tests
In vivo tests
Official regulation of testing methods (former Annex X)
Annex XI (adaptations)


Tonnage-triggered information requirements
Standard testing regime
Annex VII (1 to 10 tpa)
Annex VIII (>10 tpa)
In vitro tests
In vivo test
Official regulation of testing methods (former Annex X) still missing!
"I don't use the standard in vitro test, but an equally useful one!"
"I don't use an in vivo test, I have an in vitro replacement test!"
Annex XI (adaptations)


Tonnage-triggered information requirements
Standard testing regime
Annex VII (1 to 10 tpa)
Annex VIII (>10 tpa)
In vitro tests
In vivo test
Official regulation of testing methods
"I do have a suitable in vitro test which is good because there is no standard in vitro test !"
"I don't use an in vivo test, I have an in vitro partial replacement test and will use it in a WoE approach (XI 1.2) in combination with other data categories to fulfil the information requirements!"

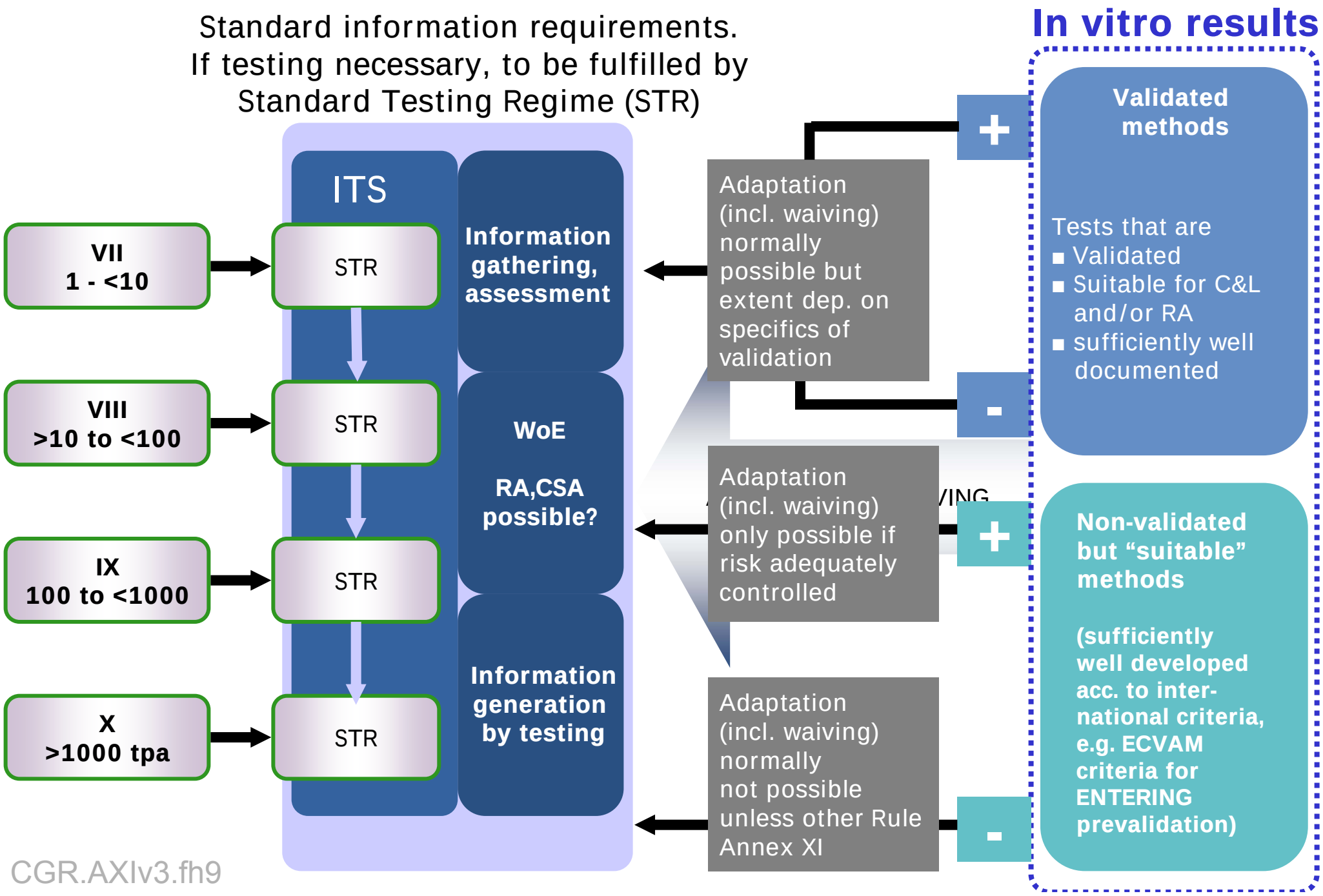
Suitable methods according to REACH

Suitable methods
(at least qualifying for pre-validation)

Everything between just entering pre-validation and just not validated

Who decides?

Validated methods


Standard information requirements.
If testing necessary, to be fulfilled by
Standard Testing Regime (STR)
In vitro results
ITS
VII
1 - <10
VIII
>10 to <100
IX
100 to <1000
X
>1000 tpa
STR
STR
STR
STR
Information gathering, assessment
WoE
RA,CSA possible?
Information generation by testing
Adaptation (incl. waiving) normally possible but extent dep. on specifics of validation
Adaptation (incl. waiving) only possible if risk adequately controlled
Adaptation (incl. waiving) normally not possible unless other Rule Annex XI
+
-
+
-
Validated methods
Tests that are
Validated
Suitable for C&L and/or RA
sufficiently well documented
Non-validated but "suitable" methods
(sufficiently well developed acc. to inter-national criteria, e.g. ECVAM criteria for ENTERING prevalidation)
CGR.AXIv3.fh9

RIP 3.3 ECVAM's contribution

- ***Stakeholder expert group (SEG) input process, Project management group:***
  Thomas Hartung, Christoph Klein

- ***Drafting group RIP 3.3:***
  Christoph Klein, Costanza Rovida, Claudius Griesinger

- ***Contribution to "endpoint working groups" (EWGs):***
  - Acute toxicity (*Laura Gribaldo*)
  - Sensitisation (*Costanza Rovida*)
  - Reproductive toxicity (*Susanne Bremer*)
  - Toxicokinetics (*Michel Bouvier d'Ivoire*)
  - Mutagenicity, Carcinogenicity (*Raffaela Corvi*)
  - Environmental/aquatic toxicity (*Marlies Halder*)
  - Skin & eye corrosion/irritation & respiratory irritation.

  (*Chaired by ECVAM*: *Valerie Zuang, Claudius Griesinger*).

OVERVIEW

The "decade of toxicology"? Are we ready ?

Evidence-based Toxicology

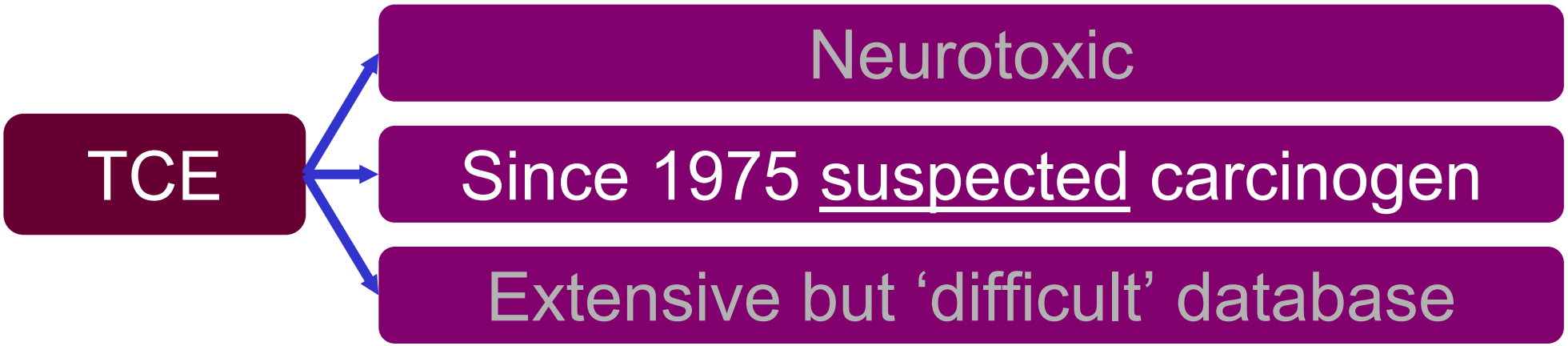
Evidence-based toxicology

Toxicology is a success story, but there is some room for improvement !

- Lack of adaptation to progress in life & toxicological sciences
- Traditional assessment methods: Unknown reliability & relevance
- Decision-making on risks & hazards: No global “best practice”, consensus-driven, en-route criteria
- Data integration – lack of quantitative and more objective methodologies
- No mechanisms to listen to societal expectations (sustainability)

Example: Risk assessment of trichloroethylene

29 risk assessments (animal & human data) analysed



Rudén C. The use and evaluation of primary data in 29 trichloroethylene carcinogen risk assessments. *Regul. Toxicol Pharmacol 2001; 34: 3-16.*

Example: Risk assessments of trichloroethylene

Carcinogen
4 studies

Equivocal
19 studies

No carcinogen
6 studies

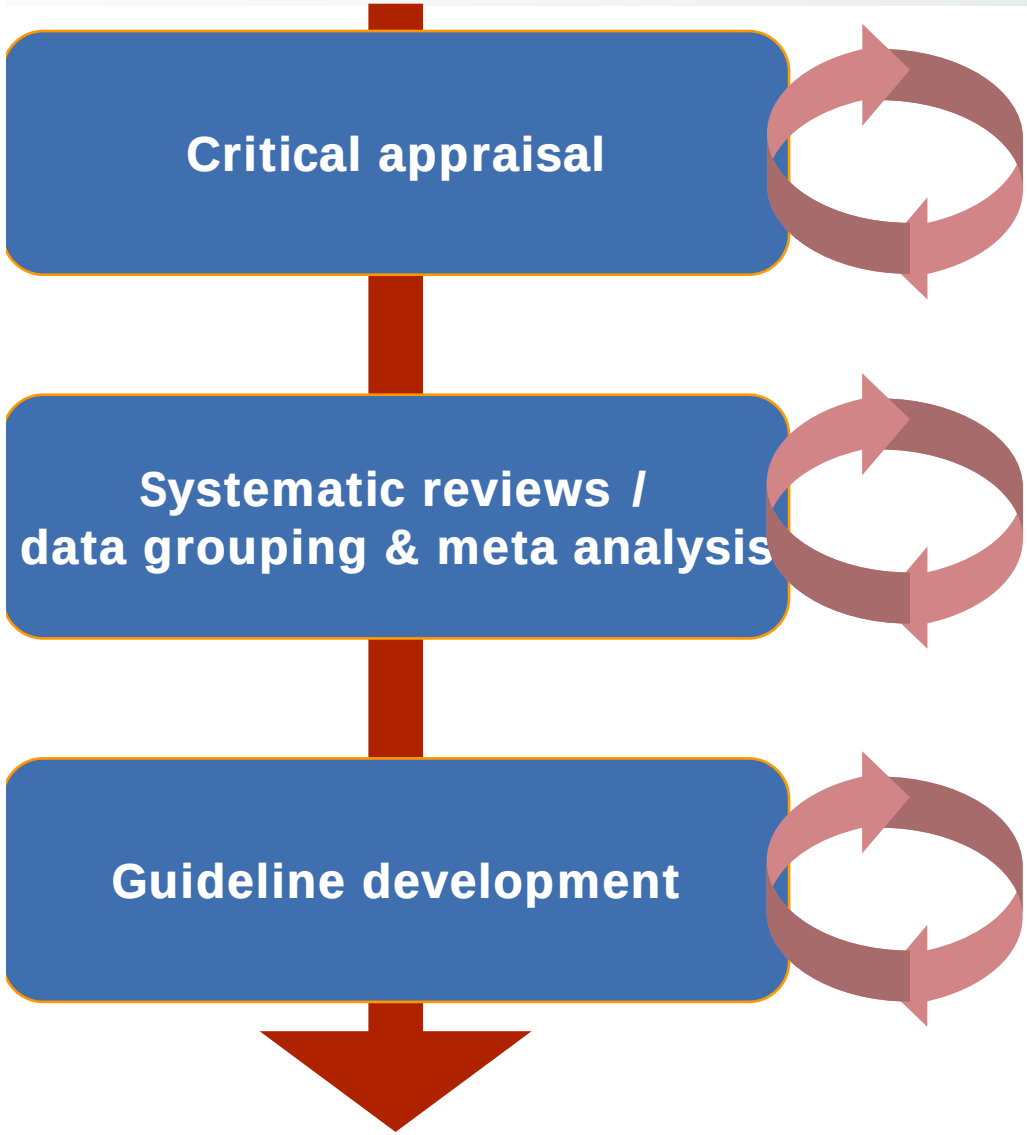
- **average reference coverage** **18%** } **selection bias**
- **average citation coverage of most relevant studies** **80%** }
- **interpretation differences of most relevant studies in** **27%**
- **study/data quality: assessment not documented in** **65%**

Reasons for differences in risk assessments

⇒ **bias in data selection (incomplete and diverse)**

⇒ **different data interpretation/evaluation**

Evidence based medicine - tools



- Continuous adaptation to scientific progress.
- Transparency.
- Explicitness.

- Conscientious, Judicious use of best "evidence".

Evidence-Based Medicine: systematic reviews

Question — How much more reliable/efficient is diagnostic method X compared to Y detect Z

Standards — Define *ex ante* criteria for **search**, **inclusion**, **evidential power** of information

Minimising intrinsic bias

"Protocol"
(Study plan, review plan)

Question

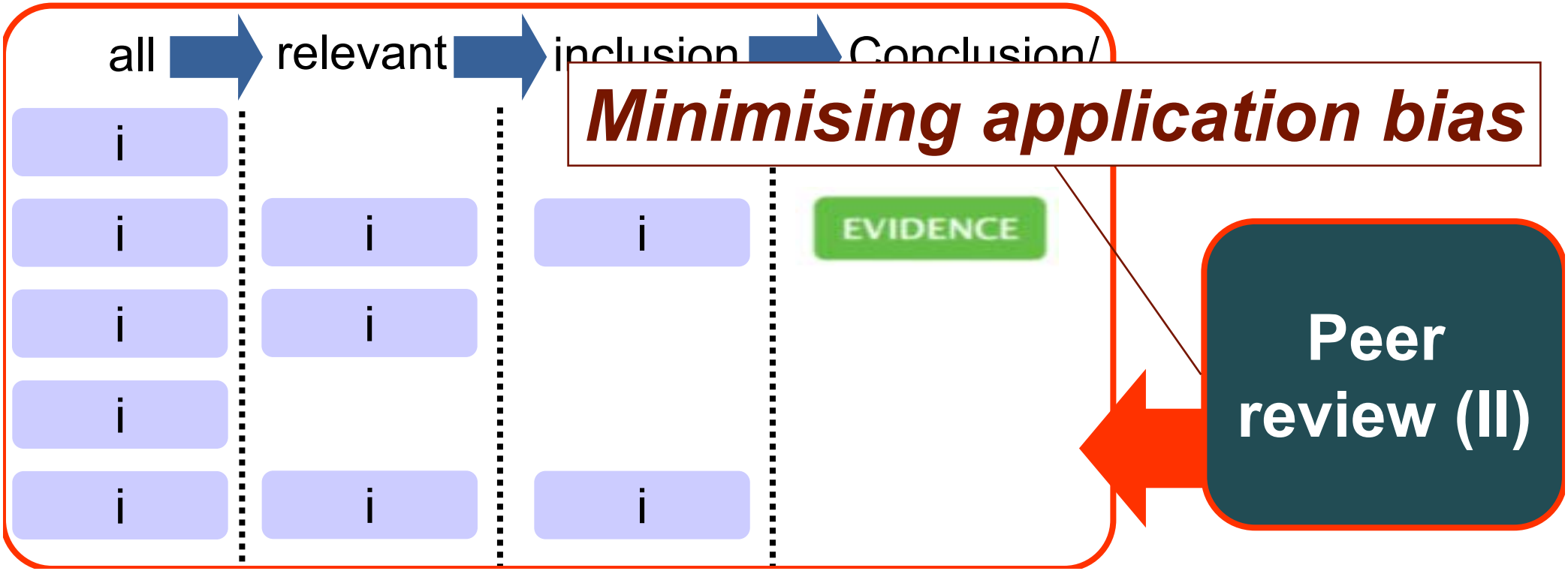
Standards

Peer review (I)

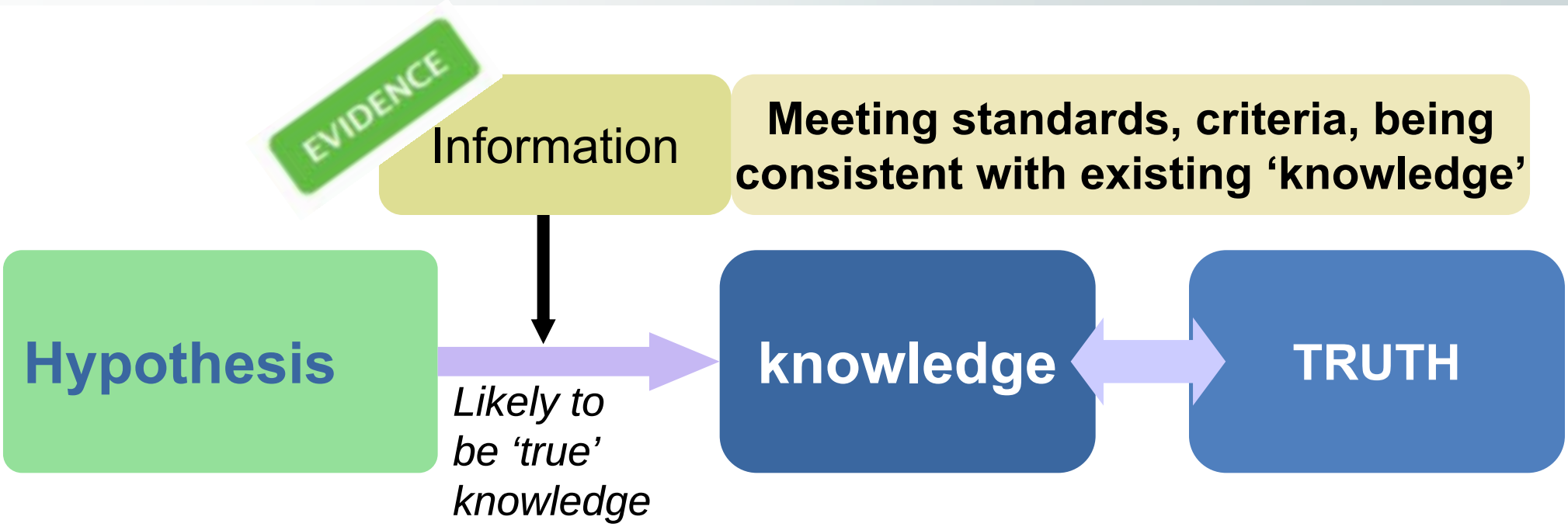
Evidence-Based Medicine: systematic reviews

Question — How much more reliable/efficient is diagnostic method X compared to Y detect Z

Standards — Define ex ante criteria for **search**, **inclusion**, **evidential power** of information



What actually is evidence ? – epistemology



- *What **criteria / standards** must **information** fulfil to be regarded as **evidence** for / against a hypothesis so that we can regard the hypothesis as **probable knowledge?***

1st International Forum towards Evidence-Based Toxicology (EBT)

15-18 October 2007, Como, Italy

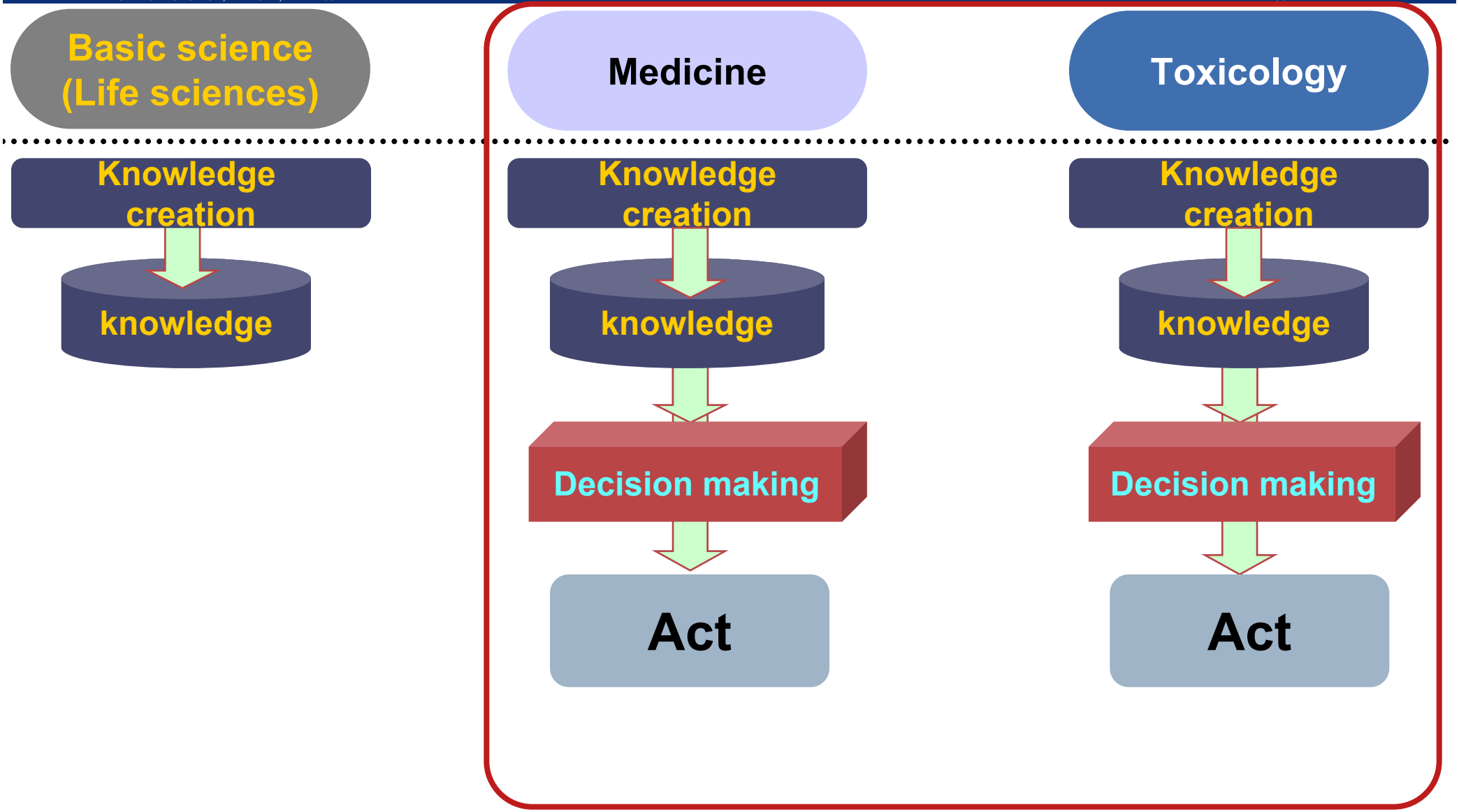
www.ebtox.org

About 170 participants

- **From basic research, industry, regulation, animal welfare, policy making…**
- **From > 25 countries**
- **From Europe, Africa, Asia, America**

Two of the core questions of the forum

- *Kaizen* : How can we further improve toxicological practice ?
- **Can toxicology profit from evidence-based approaches (e.g. EBM) ?**
- **How can we used Evidence-Based tools in Toxicology (EBT) ?**
- How do we define EBT, what are its objective and aims ?
- How can we make EBT workable ?



A craft (e.g. metallurgy)

Medicine: causation & probability

Medicine

Hypotheses on causal links (causation)

- ***Z*** ⟶ ***A*** (adverse effect)
- ***C,P*** ⟶ ***D*** (desired effect), ***A*↓**

Probability of ***A*** to **occur** (probability)
Probability of ***C*** to cause add. adverse effects ***A2***

Probability of ***C*** (cure) to reduce ***A*** (probability)
Probability of ***P*** (prevention) to avoid ***A*** (probability)

Disease, hazard

Pathogenesis

Curative/preventive acts

Risk

Effectiveness

Toxicology: causation & probability

Toxicology

Hypotheses on causal links (causation)

- ***Y*** ⟶ ***A*** (adverse effect)
- ***P*** ⟶ ***A*↓**

Probability of the ***A*** to occur (probability)

Probability of the ***P*** (RRM) to prevent ***A*** (probability)

Hazard

"Toxicogenesis"

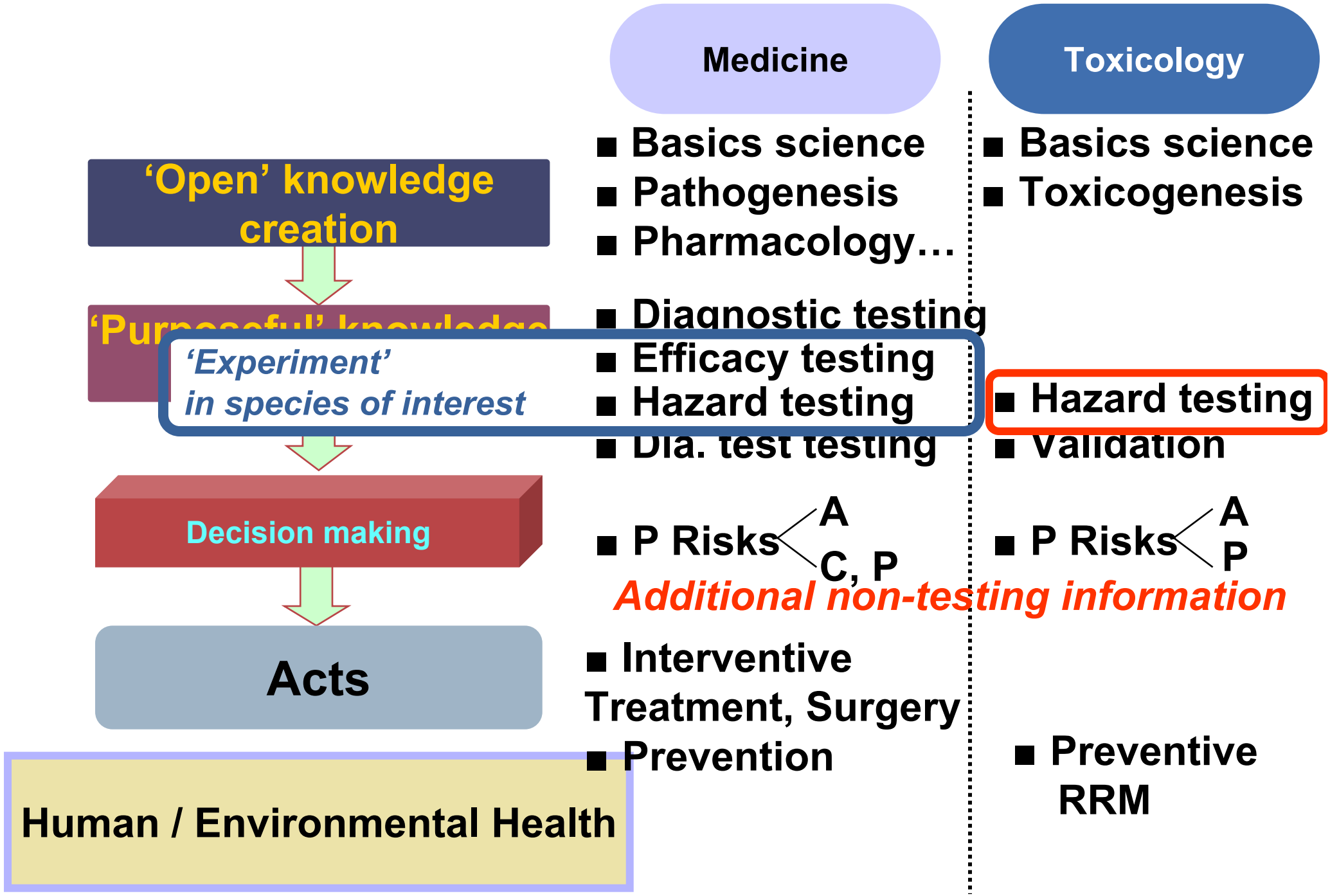
Curative/Preventive acts

Risk

Effectiveness

Core concepts: causation and probability

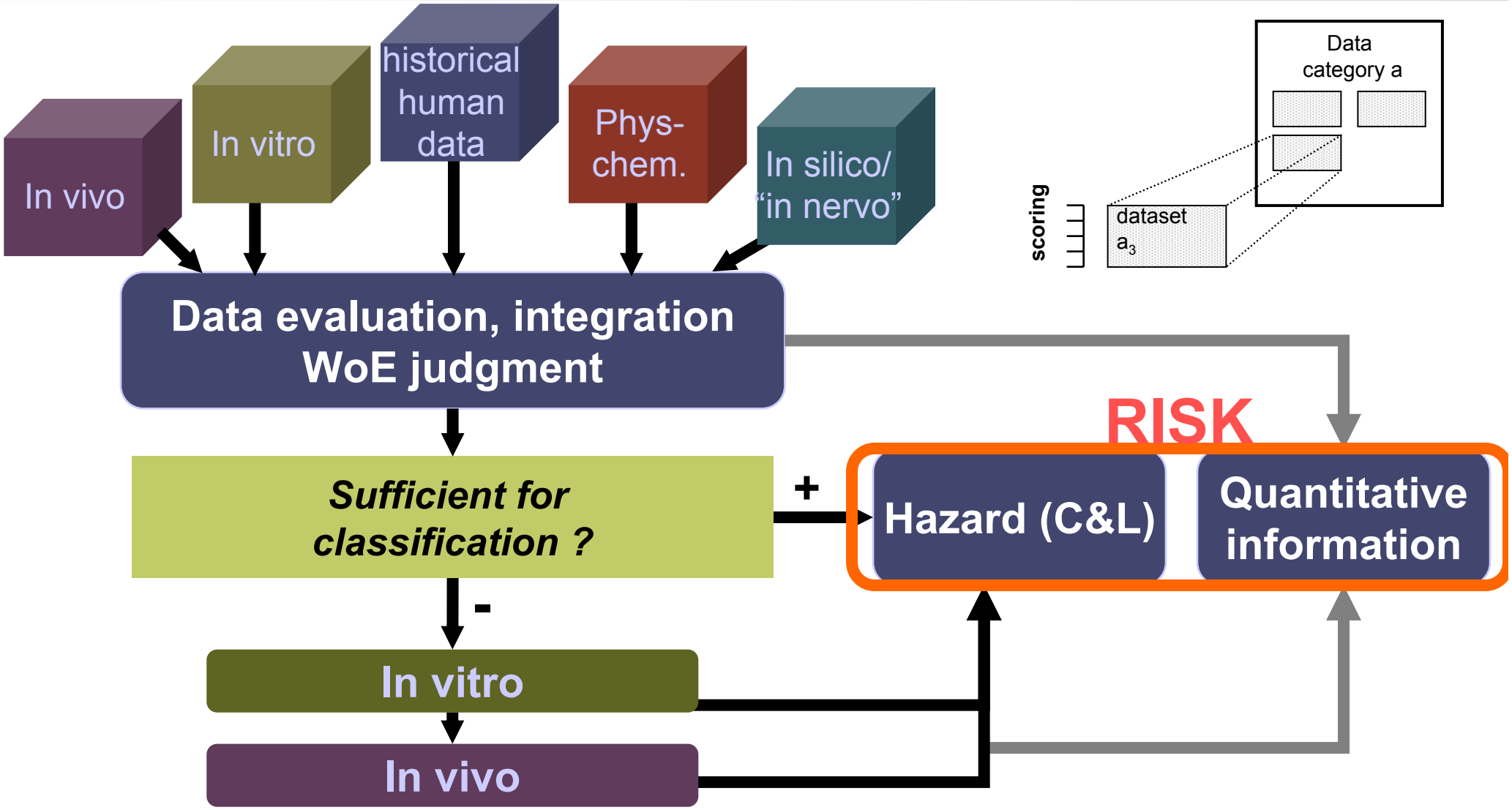
	Medicine	Toxicology
Causation	*Disease, hazard*	*Hazard*
	Pathogenesis	*"Toxicogenesis"*
	Curative/preventive acts	*Curative/Preventive acts*
Probability	*Risk (A, A2)*	*Risk (A)*
	Effectiveness	*Effectiveness*


Medicine
Toxicology
'Open' knowledge creation
'Purposeful' knowledge
'Experiment' in species of interest
Decision making
Acts
Human / Environmental Health
■ Basics science
■ Pathogenesis
■ Pharmacology…
■ Diagnostic testing
■ Efficacy testing
■ Hazard testing
■ Dia. test testing
■ P Risks A C, P
■ Interventive Treatment, Surgery
■ Prevention
■ Basics science
■ Toxicogenesis
■ Hazard testing
■ Validation
■ P Risks A P
Additional non-testing information
■ Preventive RRM

Application in toxicology ?

- Developing and applying ex ante criteria for extracting "evidential power" of information to evaluate a specific question using structured approaches (systematic reviews)
- Quantitative data evaluation for acute decision making

Quantitative assessment of data (REACH)



Results

Declaration

10 defining characteristics

Definition / mission statement

Proceedings (early 2008)

EBT symposium Eurotox, Rhodes, Greece, 2008

Facilitation steps

Dissemination

Setting up method groups

Cross-fertilization with other e.b. disciplines

OVERVIEW

Independent assessment of alternative methods

CORRELATE

CORRELATE…

- Is functional.
- Validations will be peer-reviewed. The current proposal (suggested and generally positively received by ESAC) with regard to ESAC endorsement is to update the primary ESAC statement once a similar method has been validated, but not to issue a separate ESAC statement for each similar method.
- 1st validation study starting December / January.
- Strong motivation to cooperate with national reference laboratories (to be set up – revision 86/609).

Possible roles of CORRELATE

Validation tool for similar methods

Market 'pluralism' of methods

Reference laboratory network

European added value

Prospective validation

Assessment: robustness, handling qualities

REACH suitability

Continuous REACH implementation - ECHA

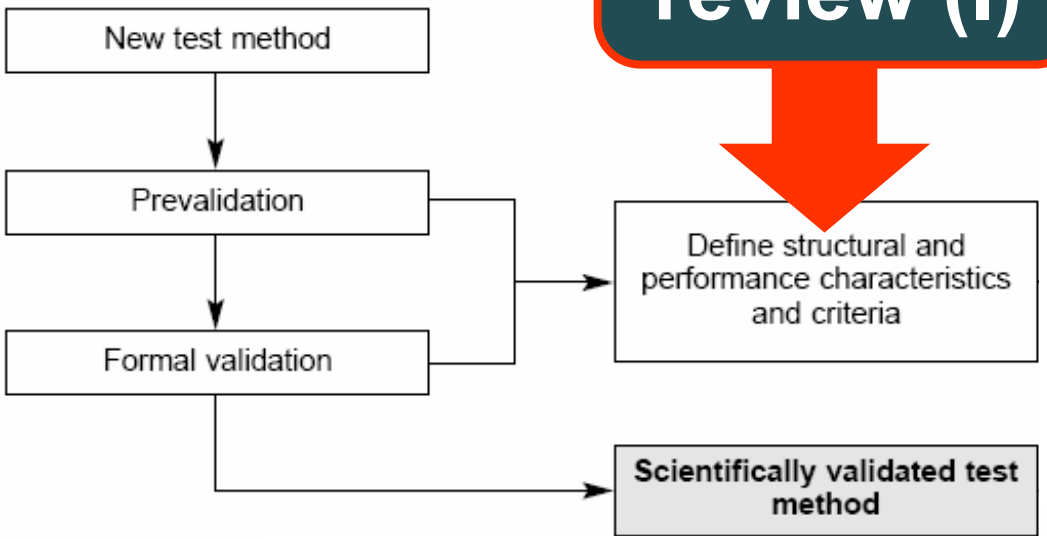
Two catch-up studies so far

Skin corrosion

1. EpiDerm (catch-up with EPISKIN) 2000
2. SkinEthic 2006
3. EST-1000 2007/8

The "classical" catch-up validation pathway

Figure 2: A schematic representat process



Peer review (I)

Peer review (II)

In the ECVAM process, a scientifically validated method is one that has been endorsed by the ECVAM Scientific Advisory Committee (ESAC). If the method is appropriate for chemicals testing, a draft Annex V guideline, incorporating the method, will be submitted to the EU Competent Authorities for Directive 67/548/EEC *for consideration for regulatory acceptance and application.*

Worth AP & Balls M

Catch-up vs me-too: between laboratory variability

Hypothesis 1: Similarity ✓

	Submitter	Correlate	Third laboratory	BLV datasets (required = 3)
SCENARIO 1	●●●			3
SCENARIO 2	●●	●		3
SCENARIO 3	●	●	●	3

"Catch-up" process

"Me too" process

ESAC peer review panel

Peer review

Validation statement

Catch-up vs me-too: between laboratory variability

"Catch-up" process

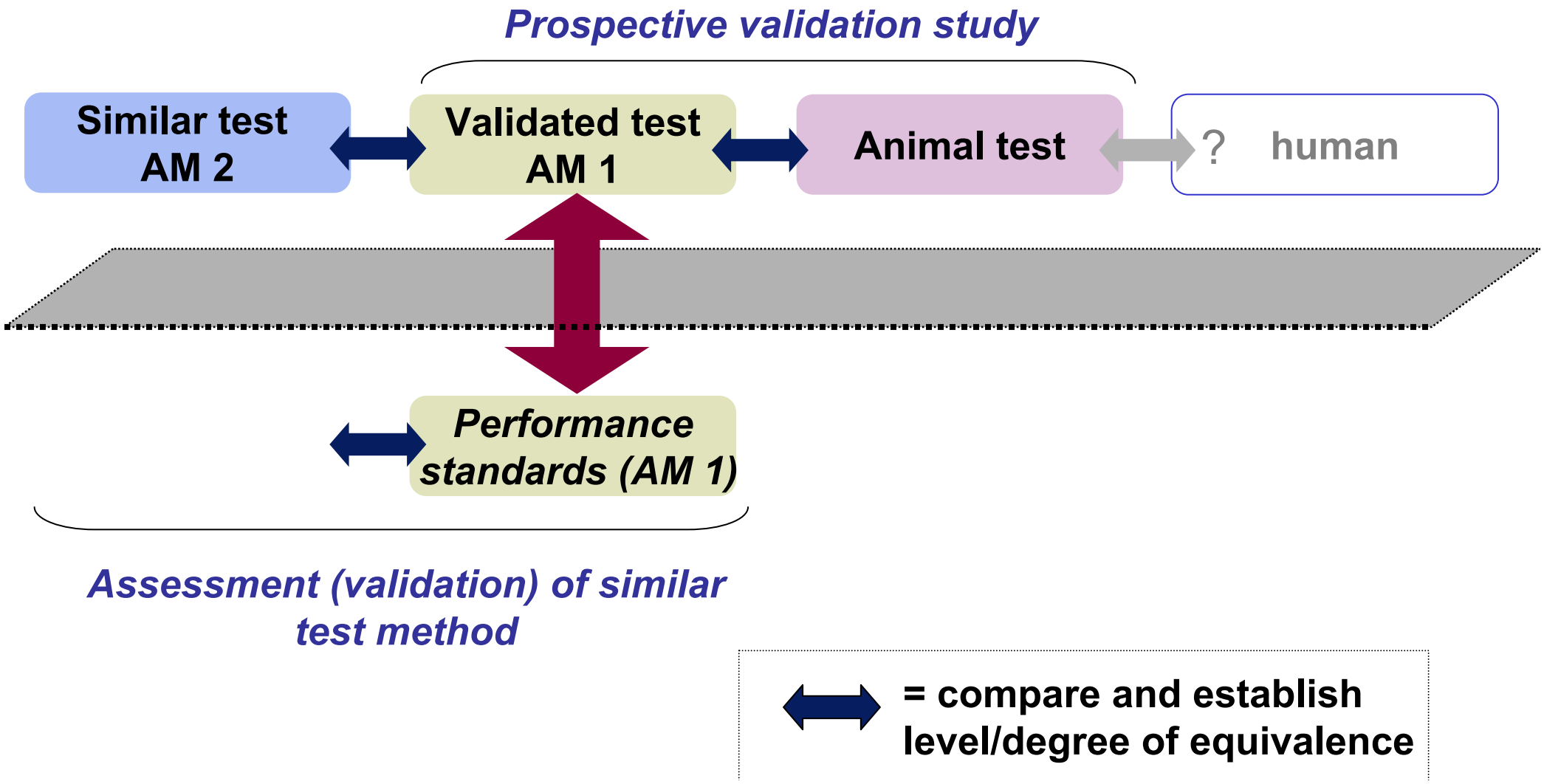
In the past:
Comparable to submissions of external validation studies. No independent laboratory involved.

In the future:
External studies coordinated by ECVAM with / without participation of NETWORK laboratory.

"Me too" process

In the future:
Studies with part of data generation by ECVAM-CORRELATE (and NETWORK laboratory)

The "validation regress" of justifications



Validation of similar methods

Performance standards

Hypothesis 1: Similarity

Conditional hypothesis !

Limited experimental set

Applicability domain

Hypothesis 2: Equal performance

Reproducibility

Predictive relevance

Validation of similar methods

Hypothesis 1: Similarity

NOT empirically testable. Justification via standards / ex ante criteria linked: Evidence-based

Conditional hypothesis !

Limited experimental set

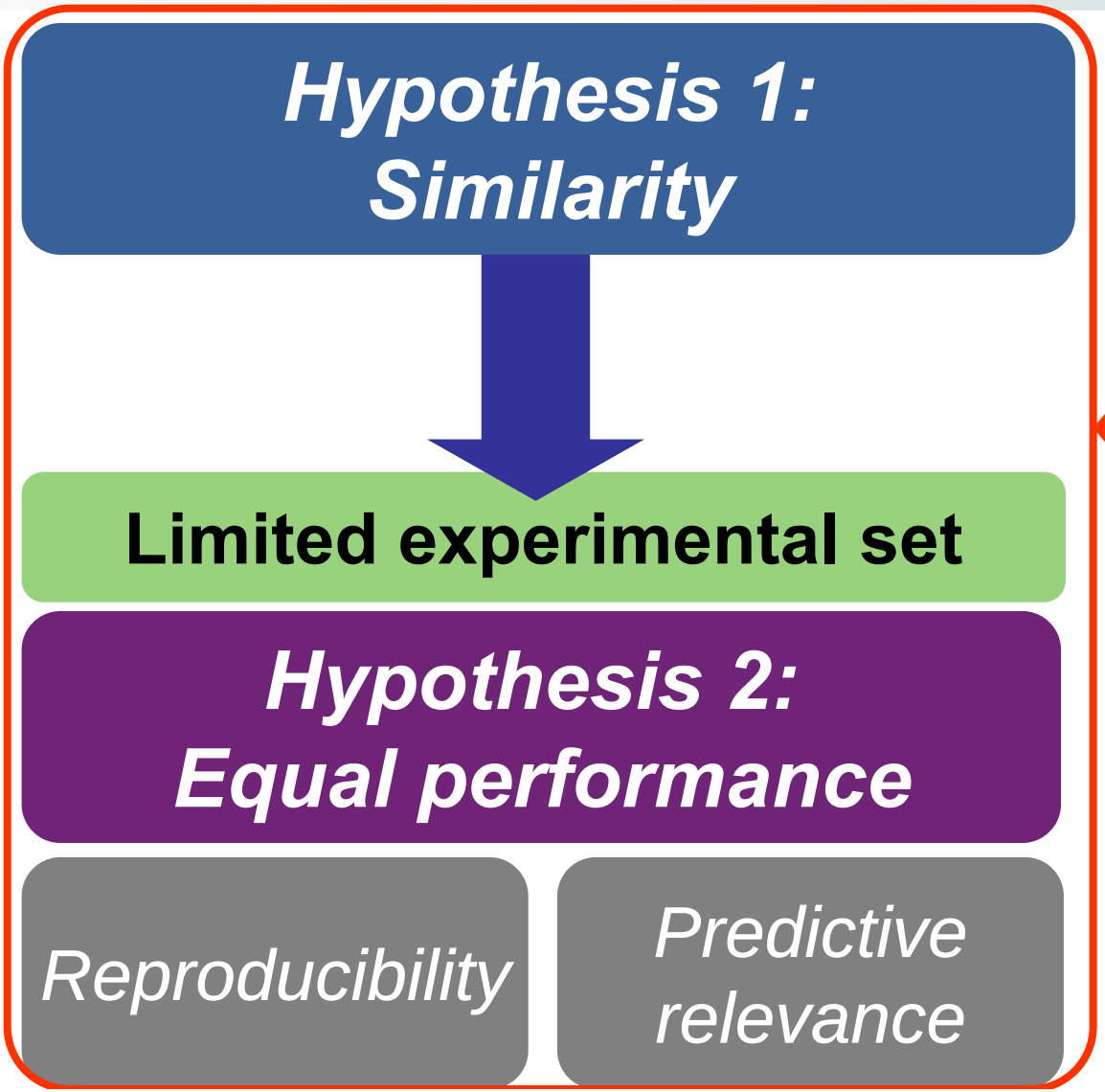
Hypothesis 2: Equal performance

Empirically testable using a limited experimental set (reference chemicals)

Reproducibility

Predictive relevance

Peer review is essential in evidence-based approaches



Key area

Peer review (II)

CORRELATE

ESAC statements for new methods might be *updated* once similar methods have been validated

ESAC statement on scientific validity of

- **New method AM1**
- **Similar method AM2**
- **Similar method AM3**
- **Similar method AM4**

version 1

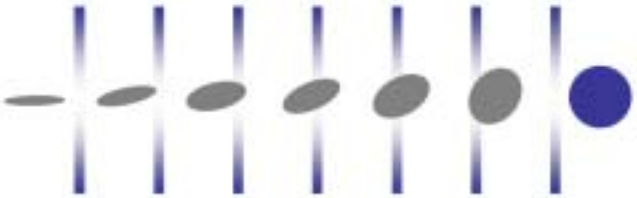
version 2

version 3

version 4

Summary (1)

CORRELATE



Similar method

catch-up track

Me-too track (CORRELATE)

Standards

Applying these standards

Similarity: non empirical

Equal performance: empirical

ESAC endorsement in form of updating original statements

Peer review ✓

Peer review

Proposal positively received by ESAC but not yet endorsed.

Thank you for your attention !