



# Zeitplan und Umsetzung der REACH-Gesetzgebung

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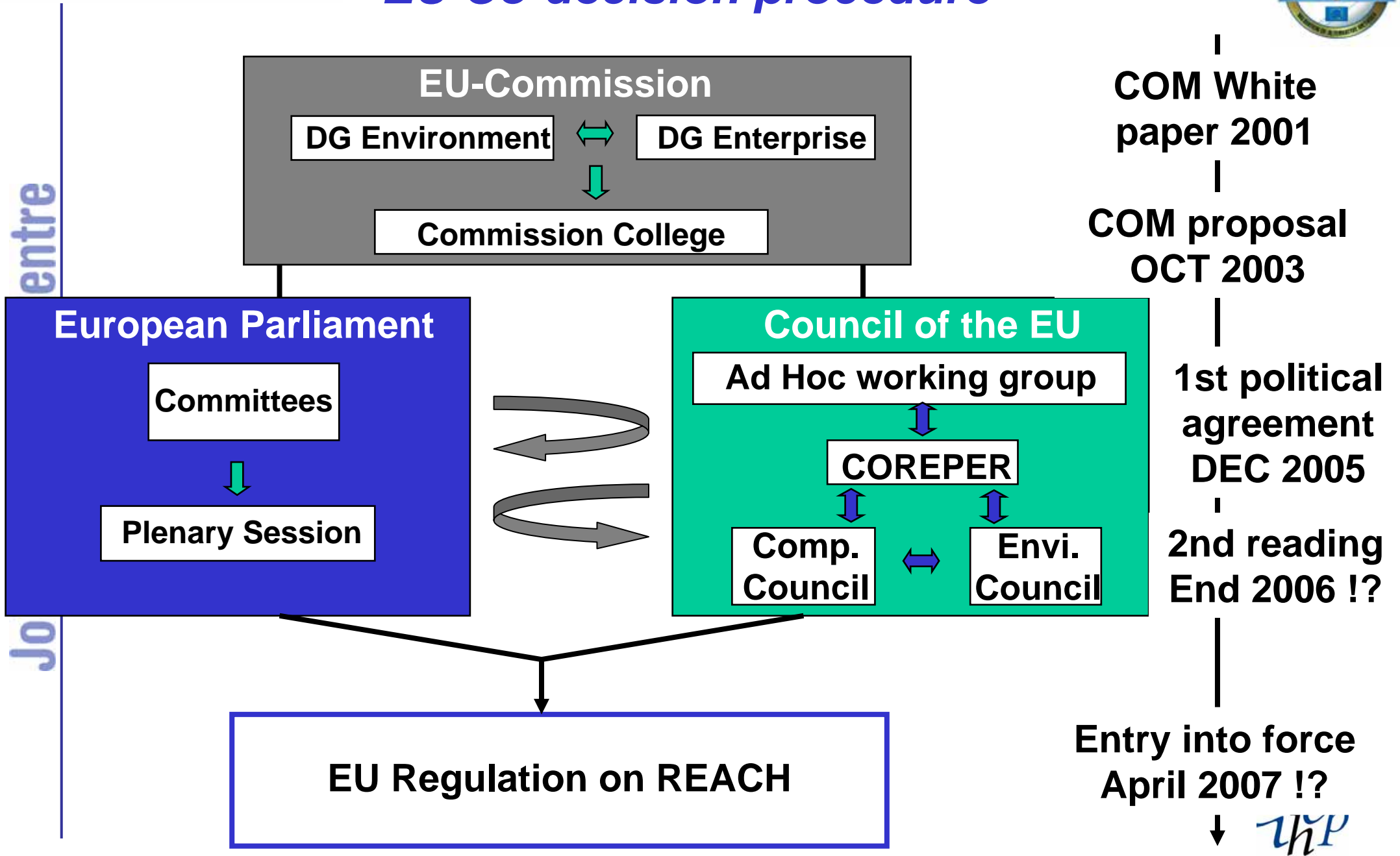
<http://ecvam.jrc.it>



# REACH

- Investment into safety of 30,000 substances: millions of animals, billions of test costs
- Most testing from 2009-2012
- Focus on validation and its acceleration
- Major impact of *in silico* and *in vitro* tests

# EU Co-decision procedure



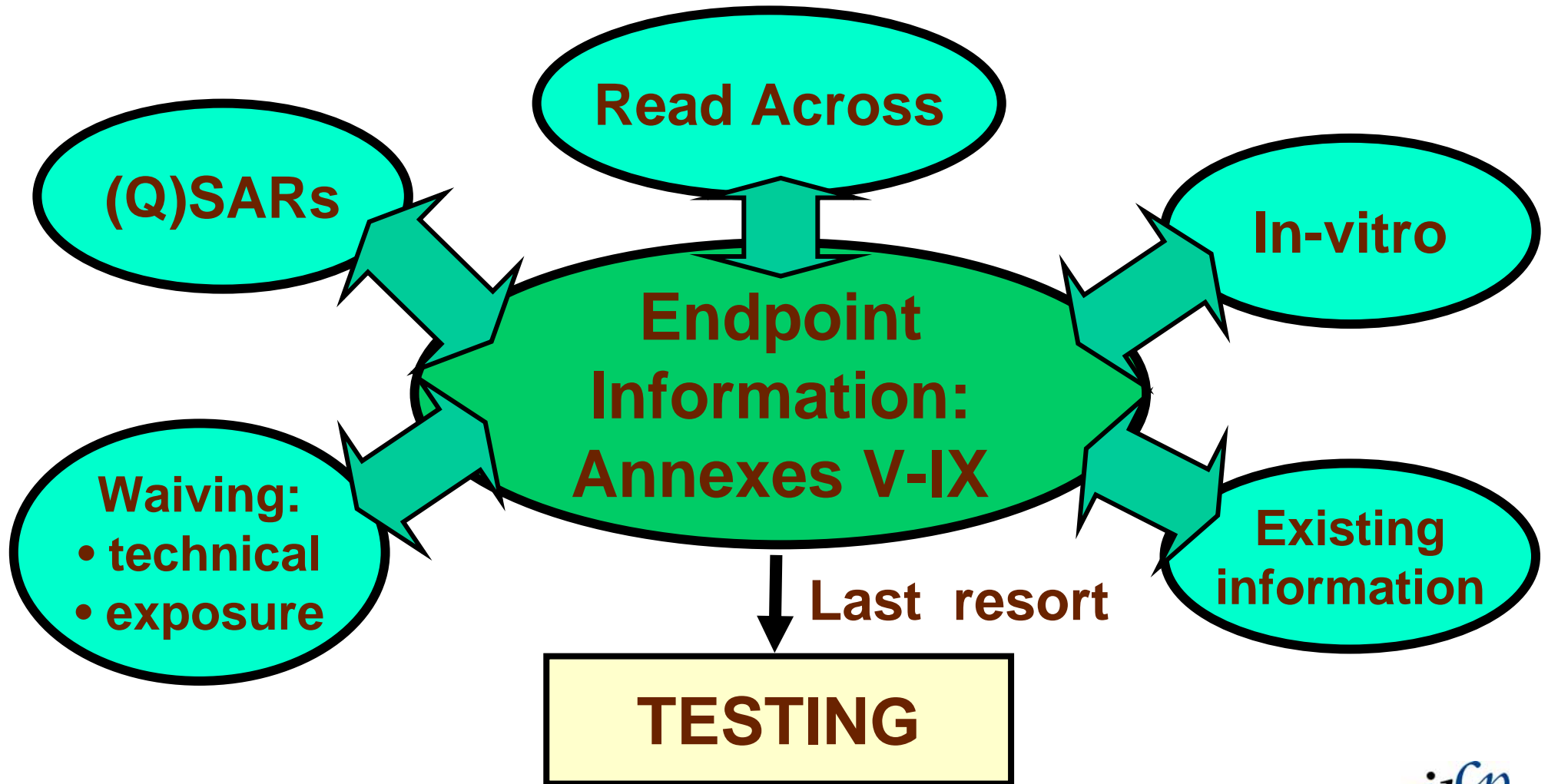
↓ *HP*



## *European Chemicals Agency*

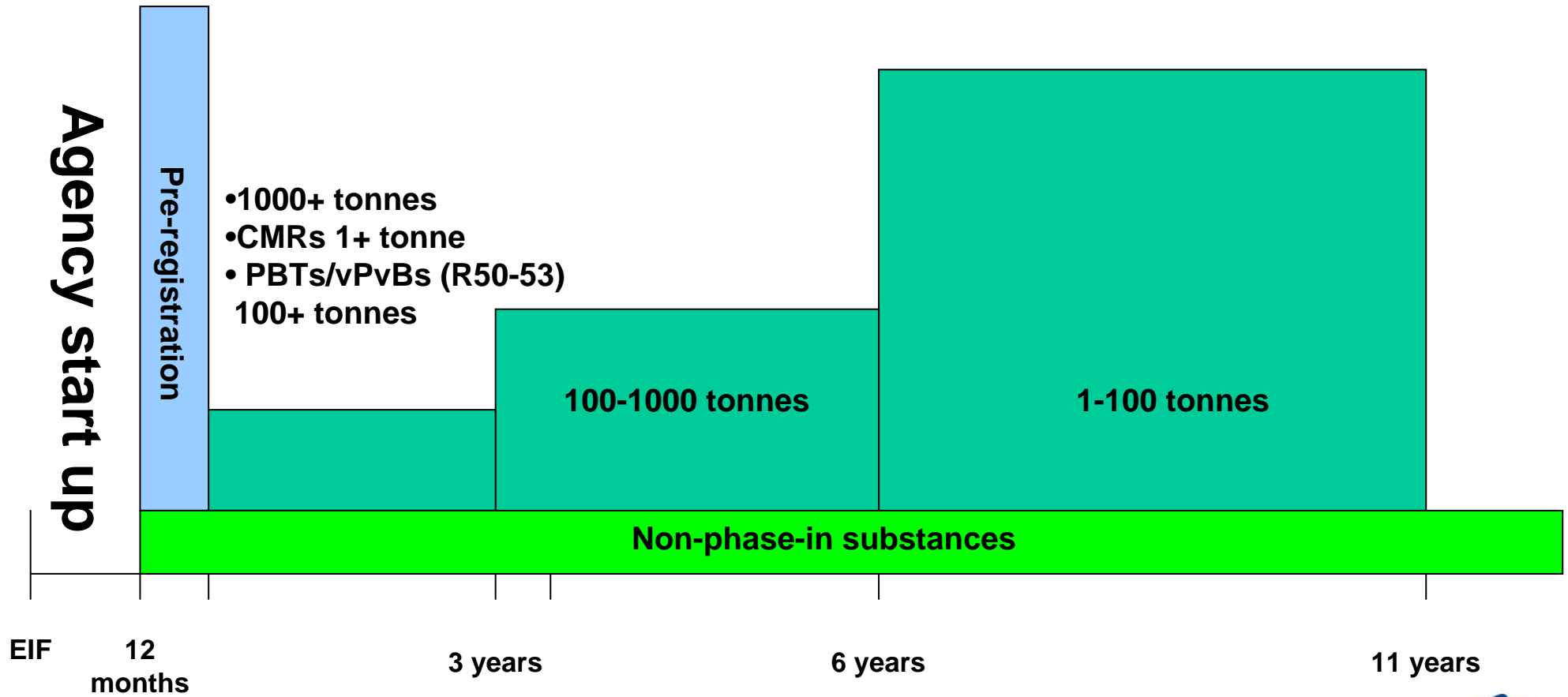
- Day to day management of REACH
  - Technical, scientific and administrative aspects
- Responsibilities:
  - Registration - reject or require completion of registration
  - Evaluation – main tasks in conduct; priority setting; coordination and harmonisation
  - Authorisation/restrictions - facilitate process; suggest priorities.
  - Secretariat for Forum and Committees
  - Deal with appeals - registration, R&D, evaluation, confidentiality
- Location: Helsinki, Finland
- Fully operational: Entry into force + 12 months (2008)
- First registrations 2010

# Registration



# Registration Overview

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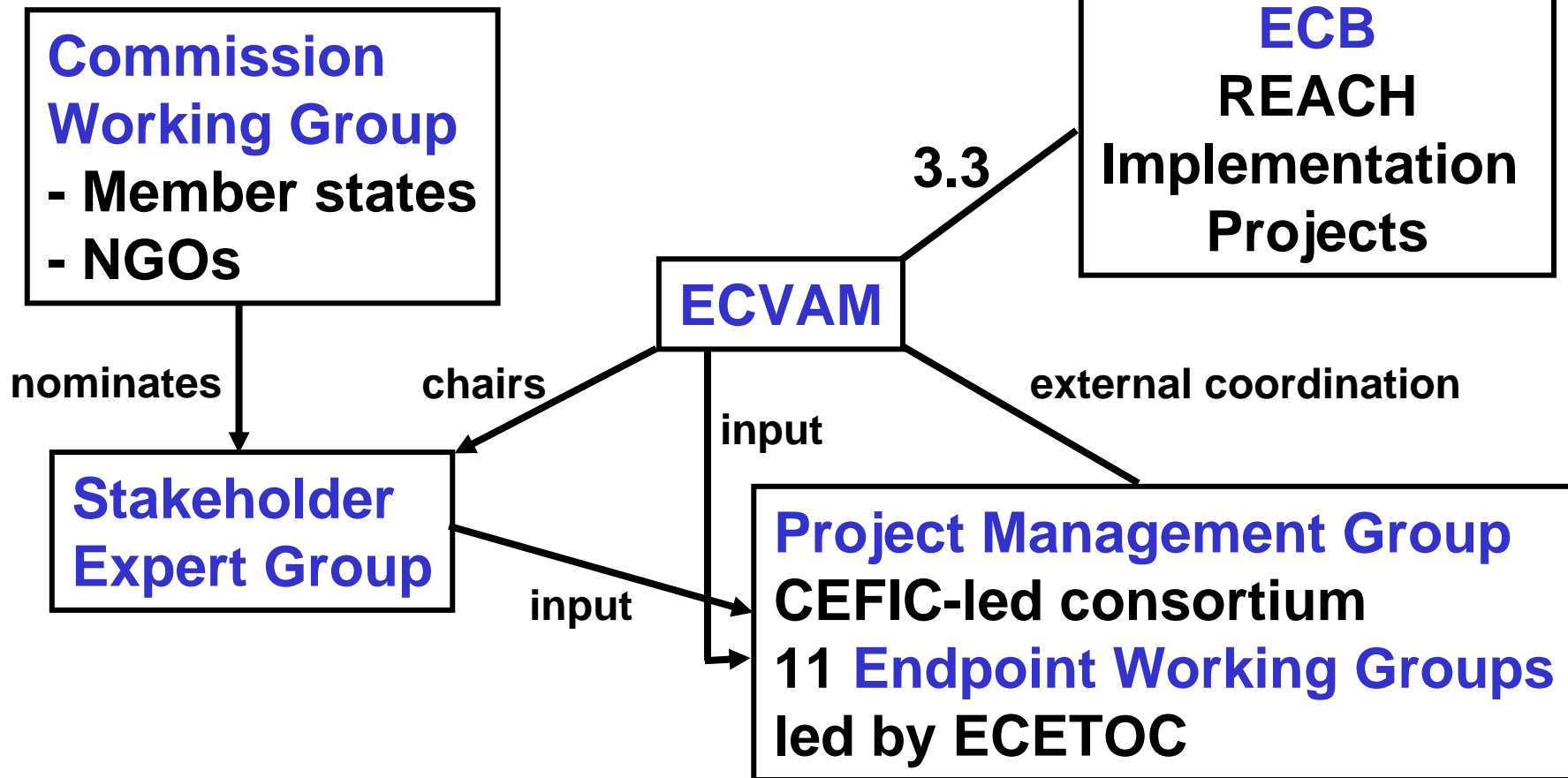


## *Commission's Interim Strategy*

- Commission's practical preparations
  - Before REACH coming into force: Jan 2004 – 2006
  - In co-operation with industry and MS
- REACH Implementation Projects (RIPs):
  - RIP 1: Process descriptions (available on ENV website)
  - RIP 2: Development of IT systems (REACH-IT)
  - RIP 3/4: Guidance Documents (industry/authorities)
  - RIP 5/6: Preparation for start-up of Agency
  - RIP 7: Commission preparations
- Strategic partnerships

# ECVAM role in RIP 3.3

ISSG: DG ENV & DG ENTR & DG JRC





## *Speeding up the process of validation*

- **Validation plus acceptance lasted 7-10a**
- **New modular approach, harmonisation with regulators and reference laboratory at ECVAM:**

**5 year process**

- **Filling the pipeline with 13 Projects  
(167 partners, 80 M€),**

**Industry Partnership EPAA**





## Status of validation of tests for REACH

	Development	Prevalidation	Validation	ESAC statement	Regulatory acceptance
Corrosion, Phototox (LLNA), tiered acute	✓	✓	✓	✓	✓
Fish acute, Embryotox, Myelotox.	✓	✓	✓	✓	
Skin Irritation, Acute Tox., Mutagenicity, Sensitisation, Eye Irritation	✓	✓	✓		
Cell transformation, Sensitisation, Endocrine Disrupters, Barrier models	✓	✓			
Percutaneous Absorption, Mutagenicity	✓				✓

# ***ECVAM: Take home message***

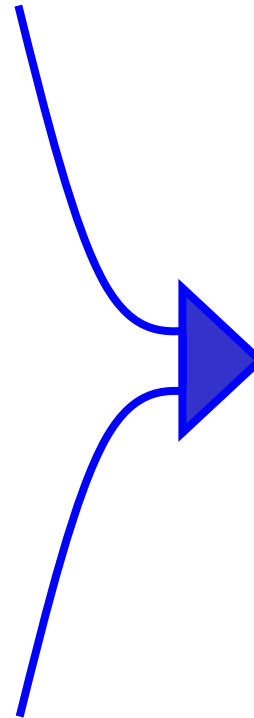
***Making cosmetics and chemicals legislation feasible***

## ***Achievements***

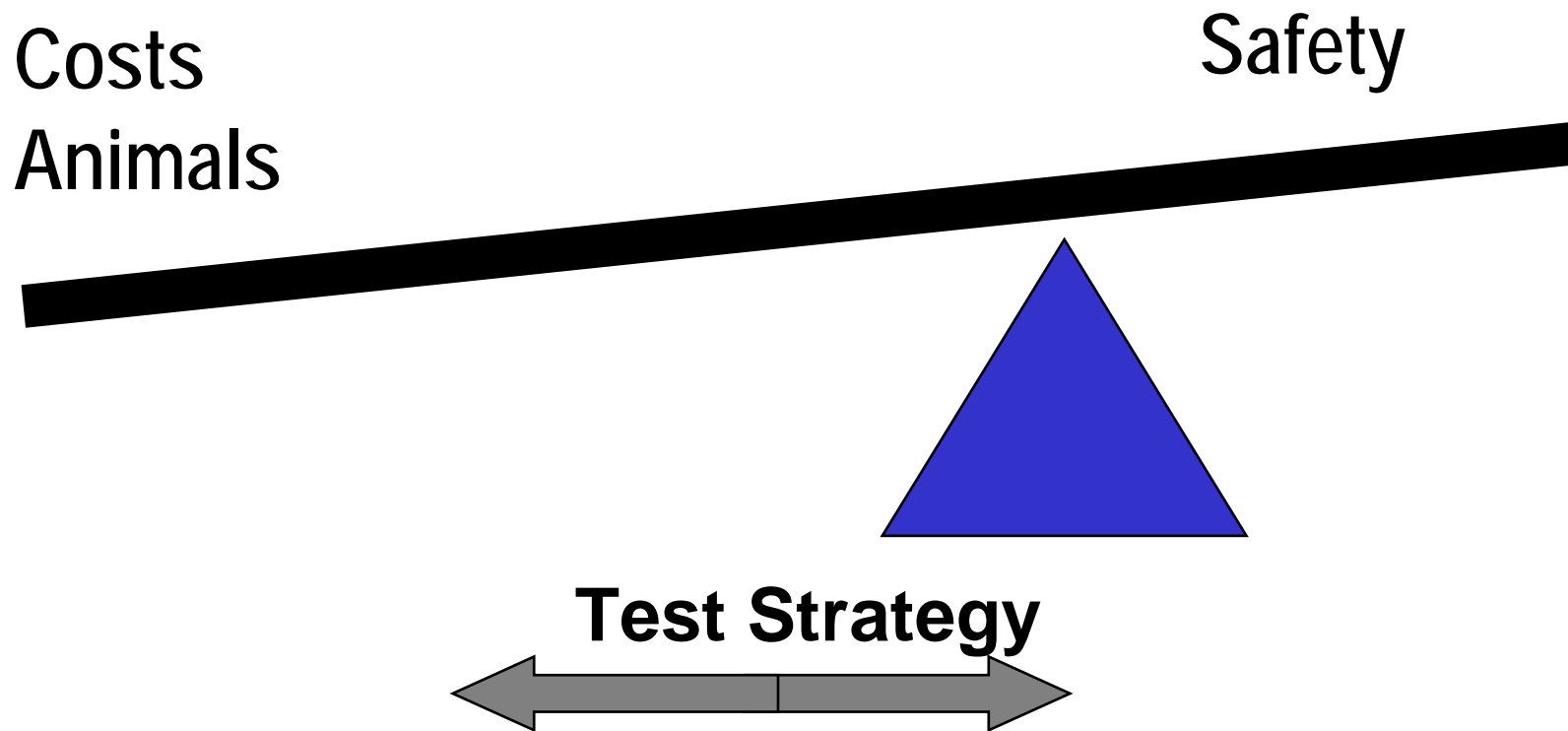
- **validation accelerated**
- **database of methods**
- **harmonisation with US & OECD**
- **network of 400 experts**
- **teaming up with stakeholders**
- **over 40 tests under validation**

## ***Goals***

- REACH**
- ➔ **Intelligent Testing Strategies**
- Cosmetics 7<sup>th</sup> amendment**
- ➔ **Phase out animal experiments in 10 years**



# *ITS purpose: finding the right balance*



# Intelligent Testing for Ecotoxicology

Joint Research Centre



**Today**  
Concentration killing 50%  
of algae, water flea and  
fish is determined (48 to 60  
fish) → lowest value

## Future



**60% less  
fish use**

Algae and water flea tested first, only lower concentration  
in fish (84% no further testing)

Validated 21 March 2006

Saving for REACH: 170.000 fish & 23 million €



## REACH ANNEX IX

### GENERAL RULES FOR ADAPTATION OF THE STANDARD TESTING REGIME SET OUT IN ANNEXES V TO VIII

#### 1.4. In vitro methods

Results obtained from suitable *in vitro* methods may indicate the presence of a certain dangerous property or may be important in relation to a mechanistic understanding, which may be important for the assessment. In this context, "suitable" means sufficiently well developed according to internationally agreed test development criteria (e.g. the ECVAM criteria for the entry of a test into the prevalidation process). Depending on the potential risk, immediate confirmation requiring testing beyond the information foreseen in Annex V or VI or proposed confirmation requiring testing beyond the information foreseen in Annex VII or VIII for the respective tonnage level may be necessary.

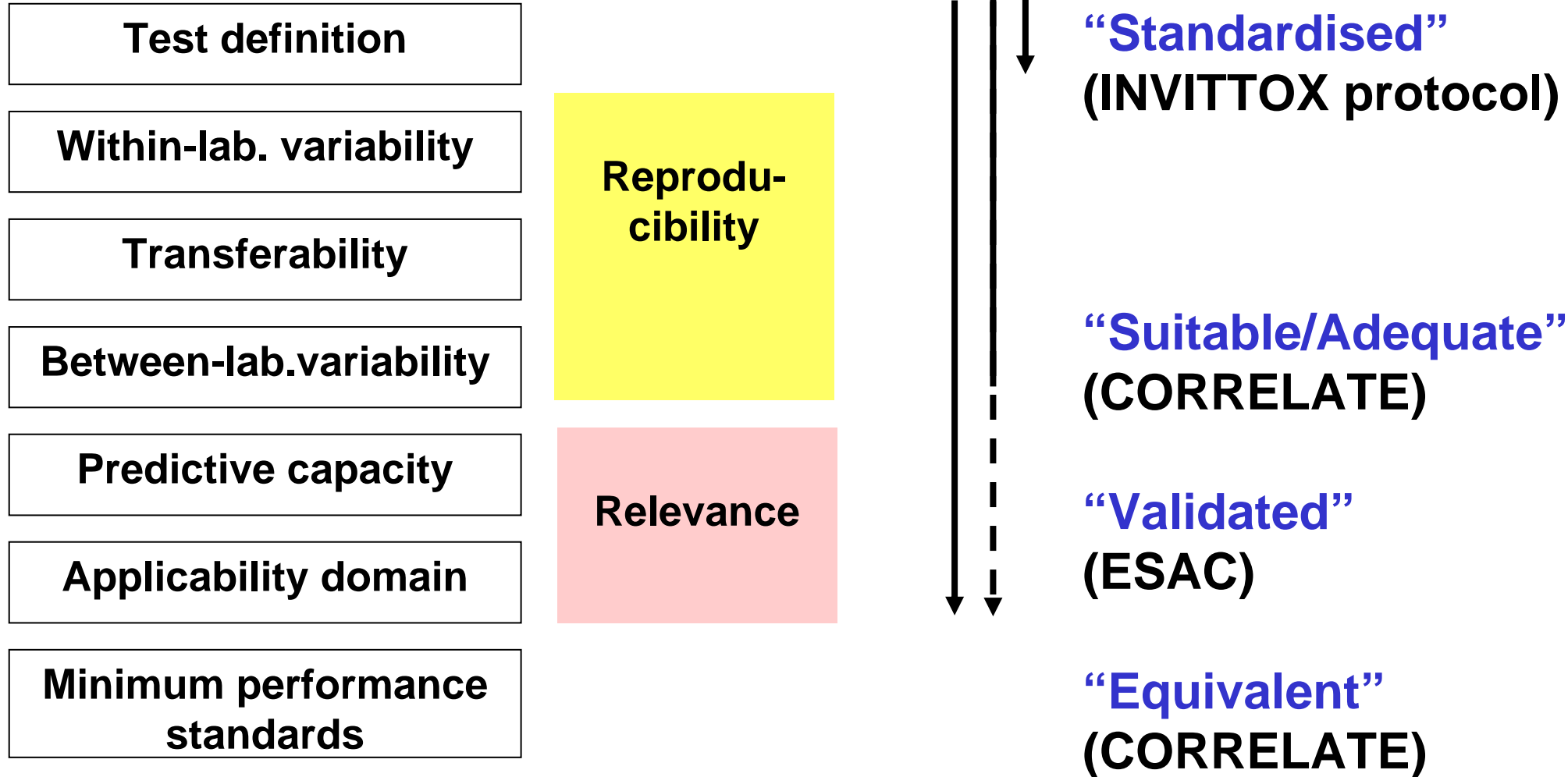
If the results obtained from the use of such *in vitro* methods do not indicate a certain dangerous property, the relevant test shall nevertheless be carried out at the appropriate tonnage level to confirm the negative result, unless testing is not required in accordance with Annexes V to VIII or the other rules in Annex IX.

Such confirmation may be waived, if the following conditions are met:

- (1) results are derived from an *in vitro* method whose scientific validity has been established by a validation study, according to internationally agreed validation principles,
- (2) results are adequate for the purpose of classification and labelling and/or risk assessment, and
- (3) adequate and reliable documentation of the applied method is provided.



# Validation modular approach



*Proposal in the context of the Commission Action plan for  
Animal Welfare 2006:*

**Community Reference Laboratory for Alternative  
Testing: CORRELATE at ECVAM**

- to speed up validation by instant start
- to show equivalence of methods similar to validated ones (“me-too”)
- to define “suitable / adequate” (not yet validated) methods for REACH



# GLP and GCCP



OECD Advisory Document No 14  
"The Application of the GLP  
Principles to in vitro studies"  
(ENV/JM/MONO(2004)26)

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GLP

ECVAM Workshop Report  
OLIVE (ECVAM laboratories)

OECD Draft Consensus Document

OECD Advisory Document No 14

1999

2000

2001

2002

2003

2004

2005

GCCP

World Conference Workshop

ECVAM Task Force Report

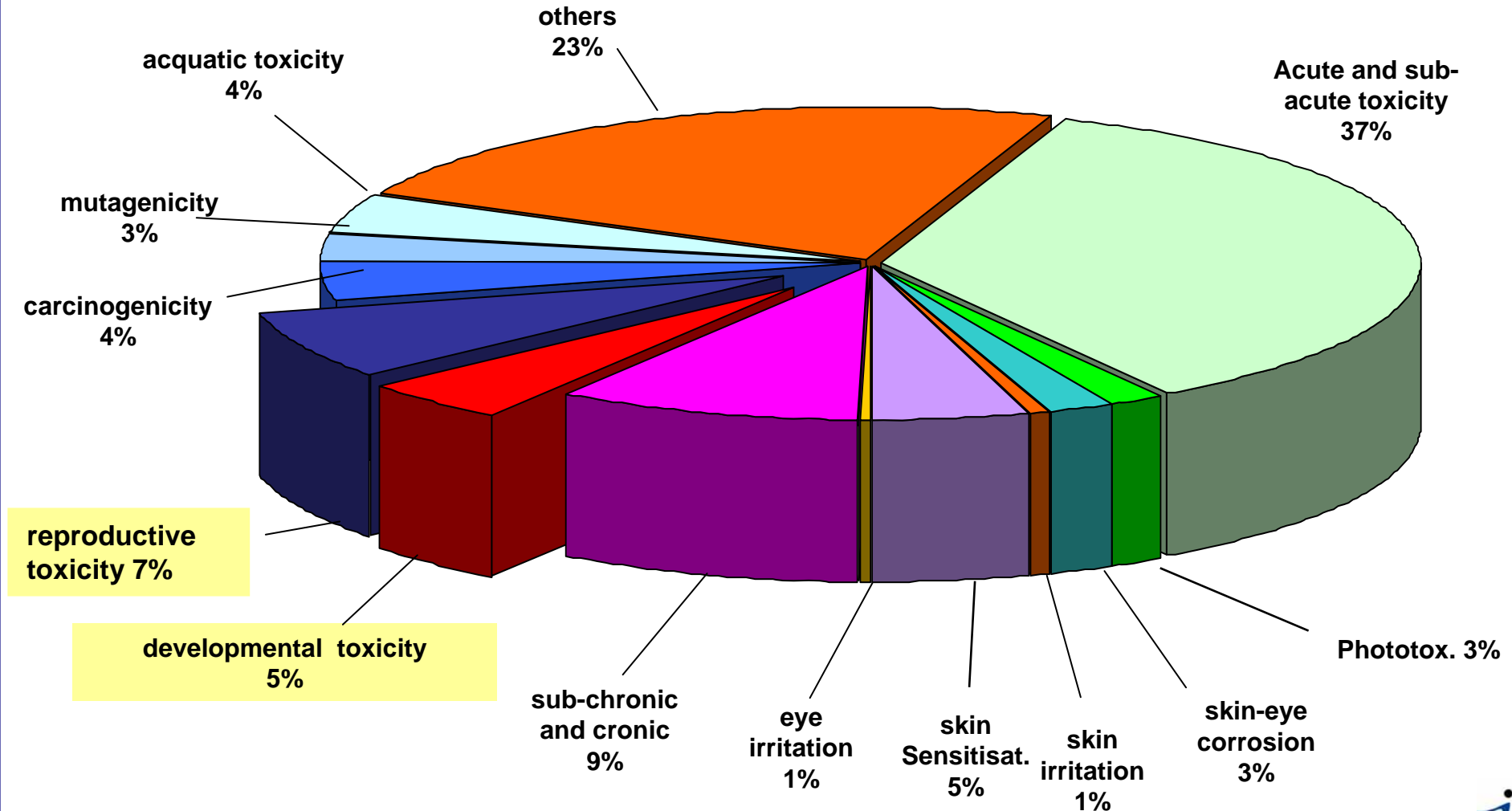
ECVAM draft Guidance Document

ECVAM final Guidance Document

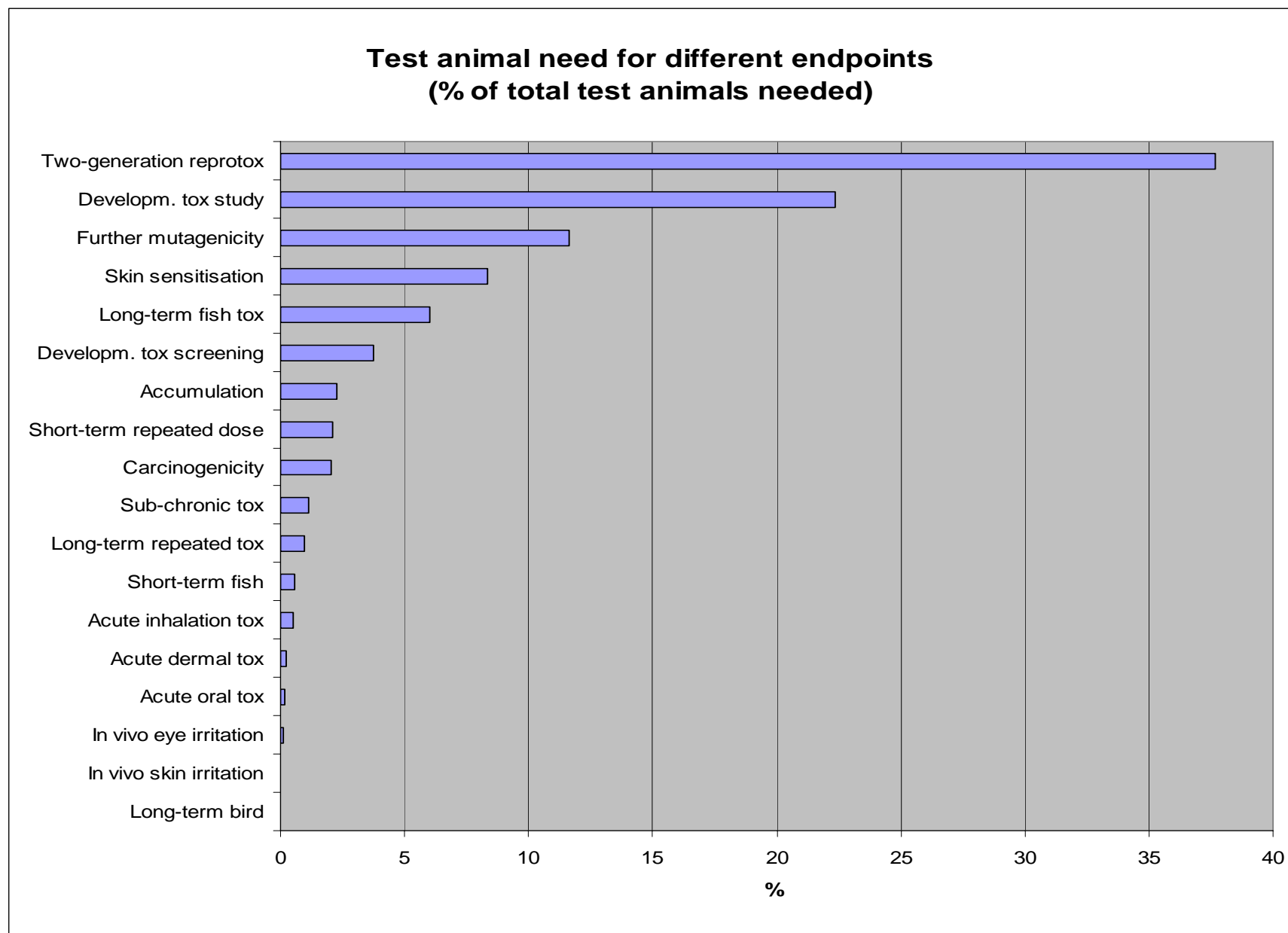
Coecke et al (2005)  
Guidance on Good Cell Culture Practice;  
ATLA, 33:261-287



# Animals used in safety evaluations in 2002



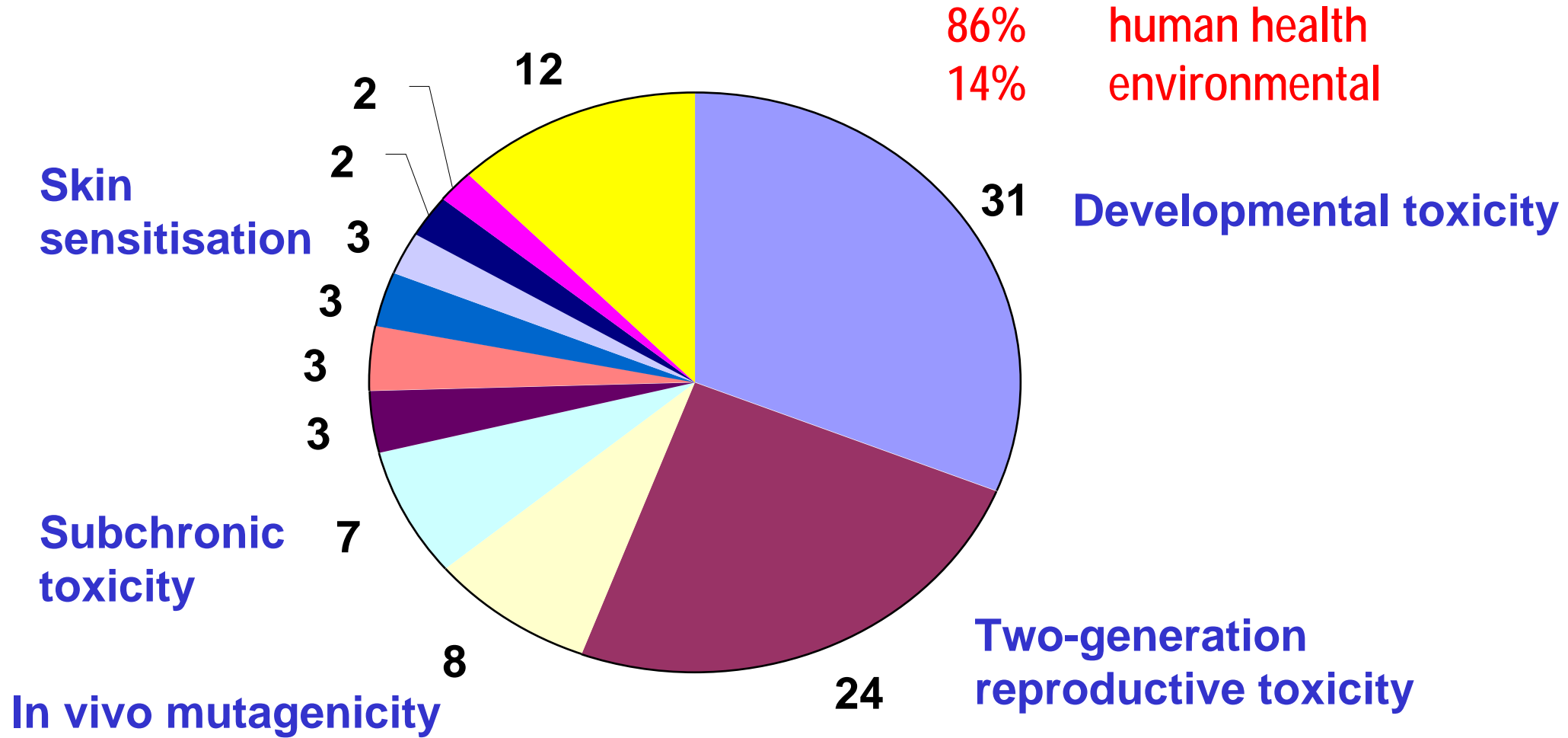
# Estimated test animal need for the different endpoints (van der Jagt et al., 2004)



# Estimated testing costs REACH (2130 M€)



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Pedersen *et al.* (2003). Assessment of additional testing needs under REACH. <http://ihcp.jrc.cec.eu.int/>



## ***REACH: Can the same tests be applied for new and existing substances?***

### **New substances**

- **No knowledge about toxicity**
- **Low established commercial value**
- **Problem of false-negatives**

### **Existing substances**

- **Experience from use**
- **High commercial value**
- **Problem of false-positives**

# Calculation consequences of 2-generation studies for 1000 chemicals (assuming 2.5-5% prevalence, 60-85% accurate tests)

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	5%	60%	60%	70%	80%	85%	
	Human	1 <sup>st</sup> spec.	2 <sup>nd</sup> spec.	Total	Total	Total	Total
	50 +	30 +	12 +	42 +	45 +	48 +	49 +
	↗ ↘	↗ ↘	↗ ↘				
	20 f-	8 f-	8 f-	8 f-	5 f-	2 f-	1 f-
	↗ ↘	↗ ↘	↗ ↘				
	950 -	380 f+	228 f+	608 f+	485 f+	342 f+	264 f+
	↗ ↘	↗ ↘	↗ ↘				
	570 -	342 -	342 -	342 -	465 -	608 -	686 -
	↗ ↘	↗ ↘	↗ ↘				
	25 +	15 +	6 +	21 +	23 +	24 +	24 +
	↗ ↘	↗ ↘	↗ ↘				
	10 f-	4 f-	4 f-	4 f-	2 f-	1 f-	1 f-
	↗ ↘	↗ ↘	↗ ↘				
	975 -	390 f+	234 f+	624 f+	497 f+	351 f+	271 f+
	↗ ↘	↗ ↘	↗ ↘				
	585 -	351 -	351 -	351 -	478 -	624 -	704 -

*ifsp*



## *Problem Reproductive Toxicity*

- Dominant test demand: 80% of animal use in REACH (12 million) for 5.500 substances
  - Lacking capacities and experience (e.g. only 70 two-gen-studies in 25 years)
  - Limited predictive value (60-70% between species)
  - High proportion of false-positive results
- ➔ **REACH could lead to many follow-up studies for valuable existing substances**
- Need for new test strategies**

## *How we like to spell REACH after introduction of ITS*

- R** - Reasonable
- E** - Economical
- A** - Assessment
- C** - of Chemicals
- H** - with Humane  
methods