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Alternative methods already in existence for the REACH implementation

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REACH

30,000 chemicals > 1 t per year to be assessed

Various Estimates:

- ⇨ **Costs:** 2,4 (ECB) – 8 (MRC) billion €
- ⇨ **Animal numbers:** 3,9 (ECB) – 43 (BfR) million
- ⇨ **Time foreseen:** 11 (ECB) – 40 (MRC) years

Calulated savings up to 70% of costs and animal numbers, if intelligent testing strategies are applied (i.e. read-across, QSAR, in vitro, refined in vivo).

billions of Euro, millions of animals, decades of testing

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Europe goes alternative

Conference, Brussels, 7th of November 2005

- **Hosted by Commissioners G. Verheugen (DG ENTR) and J. Potocnik (DG JRC / DG RTD)**
- **Opinion leaders from politics, science and industry**
- **300 participants**
- **A portfolio of activities in Europe**
- **European Partnership**

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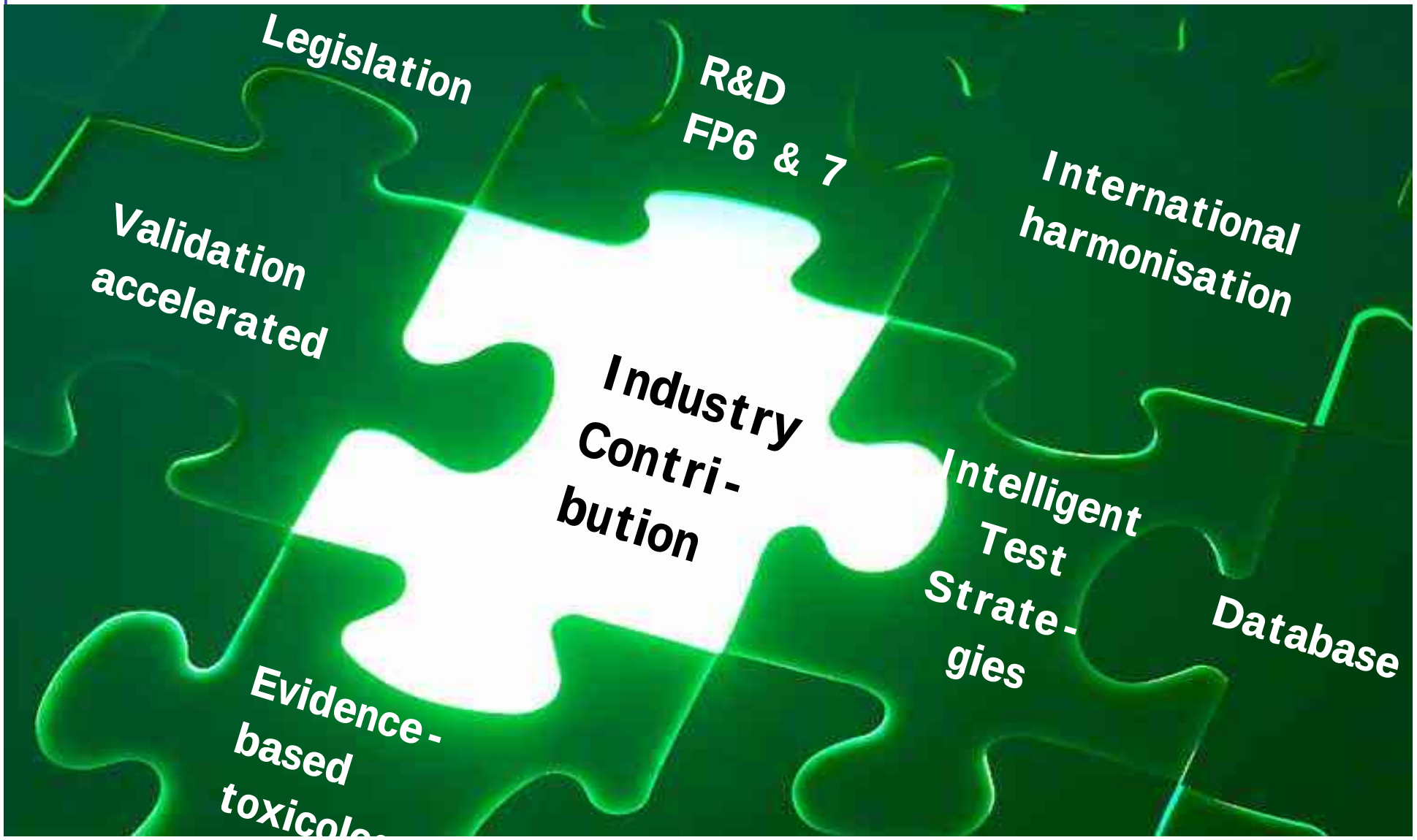
The field of alternative approaches in 2005



Meeting the timelines of the 7th amendment & REACH

> 3a **3 + 2a** **2a (+ 3a)**

Resulting last possible entry into validation:

2009 deadline: 2002

2013 deadline: 2006

Consequences:

Focus on validation not new developments

Speed up the process

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Speeding up the validation process

- **Modular approach (2004)**
  - retrospective validation
  - separation of reproducibility and predictive capacity testing
- **Reference Laboratory**
- **Accelerated peer-review**
- **Collaboration with regulators**

iccvam niceatm OECD

Resulting last possible entry into validation:

2009 deadline: 2005

2013 deadline: 2009

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The new dimension of development of alternative methods

DG RTD

DG JRC
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Policy-DGs
ECB (DG JRC)

Collaboration in 3 Integrated Projects

(about 90 partners & 30 million Euro)

“A-Cute-Tox”, “ReProTect” & “Sens-it-iv”

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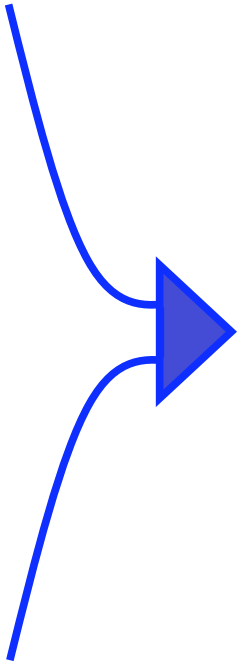
JRC: ECVAM Validated Alternatives

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 7th amendment

➔ Phase out animal experiments in 10 years

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The gift from validation to life sciences

Validation of alternative tests is one of the rare examples of quality assurance in biomedical research (relevance, not only reproducibility)

"Evidence-based medicine goes in vitro!"

Evidence-based Toxicology
= know how good the test is, which you apply

Tools:
- **Validation studies**
- **Quality assurance (GLP, GCCP)**
- **Systematic review & Meta-analysis**

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Towards an Evidence-based Toxicology

Expert-based vs. evidence-based toxicology

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Topical Toxicity and Skin Sensitisation

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

Even very good tests do not suffice for rare effects

Thought starter:

- **Healthy European without HIV risk factors: Infection rate is 1:10.000**
- **The result of 99.9% accurate test is positive**
- **Testing 10.000 people with this test will result in 1 real-positive but 10 false-positive**
- **Probability of HIV infection: 1/11 = 9%**

➡ **In toxicology frequencies of toxic effects and accuracy of tests are often unknown but same problem occurs**

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**

Limitations of current animal tests

Example Reproductive toxicity:

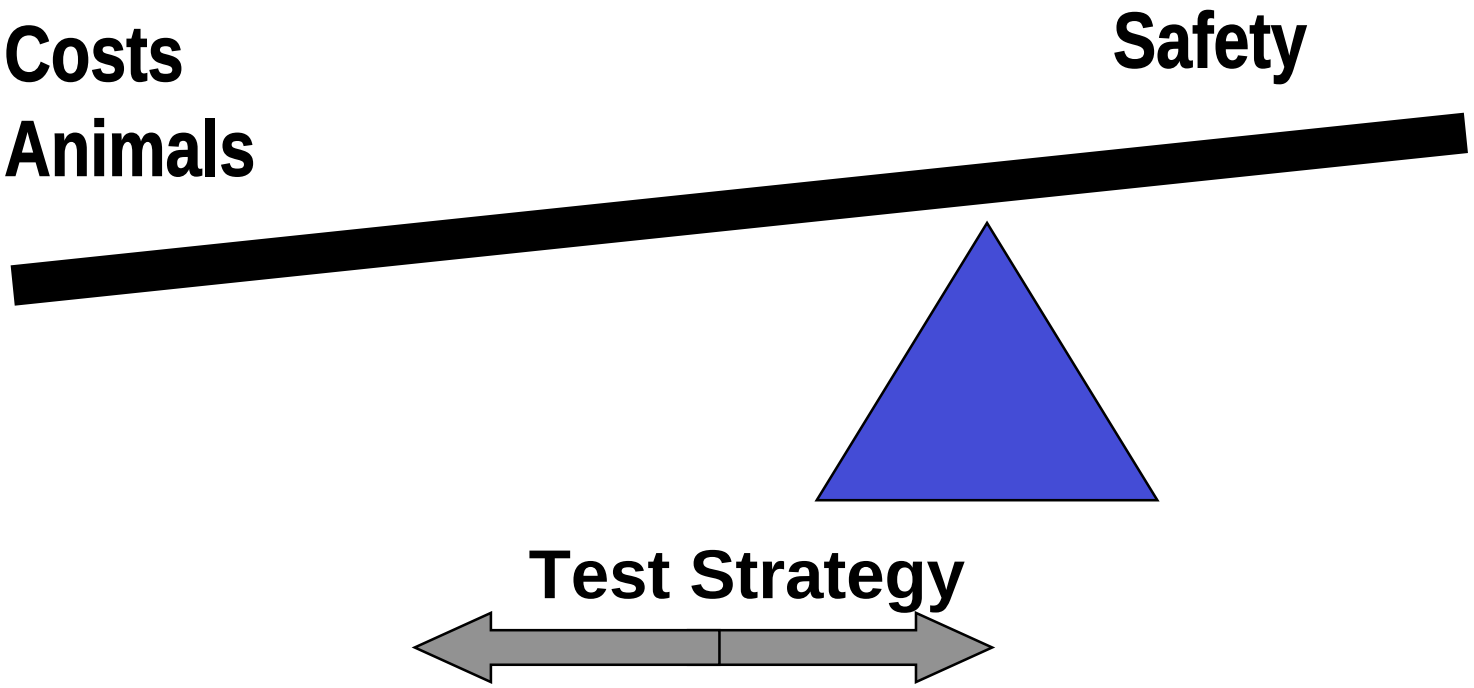
- **85% of animal use in REACH (17 million) for 5.500 substances**
- **1% real positive substances, 71% correct prediction between species (Bailey 2005)**
- **Result: 55 real-positives and 1500 false-positives**

➡ **REACH will produce an enormous number of false-positives leading to follow-up studies for valuable existing substances**

Why Testing Strategies instead of tests?

- **Single tests can be optimised only to reduce either**
  false-positive (economical problem)
  or
  false-negative (safety problem)
  results
- **Optimise work, costs, animal numbers and safety**

ITS purpose: finding the right balance



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Components of Intelligent Testing Strategies

- **Use of existing data**
- ***In-vitro* tests**
- **Optimised *in-vivo* tests**
- **Thresholds of toxicological concern**
- **SARs / QSARs and modelling**
- **Read-across and chemical categories**
- **Exposure assessment/exposure-based waiving**

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ITS for Reprotox?

- **Review *in vivo* test and prevalence**
- **Review of alerts triggering in vivo**
- ***In-vitro* battery corresponding to alerts**
- ***In-vitro* screening for endocrine disrupters**
- **Substitution of 2nd species by embryotox**
- **Lower (2nd) species (e.g. FETAX)**
- **Thresholds of toxicological concern, placenta barrier**
- **Fill conceptual framework (OECD) in ReProTect**
- **Waiving, Read-across and chemical categories**
- **Exposure-based waiving**

An Intelligent Testing: Ecotoxicology



Today

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

Future


→

→ **60% less fish use**

Algae and water flee tested first
only lower value then tested in 10 fish
only 16% of substances require further fish tests

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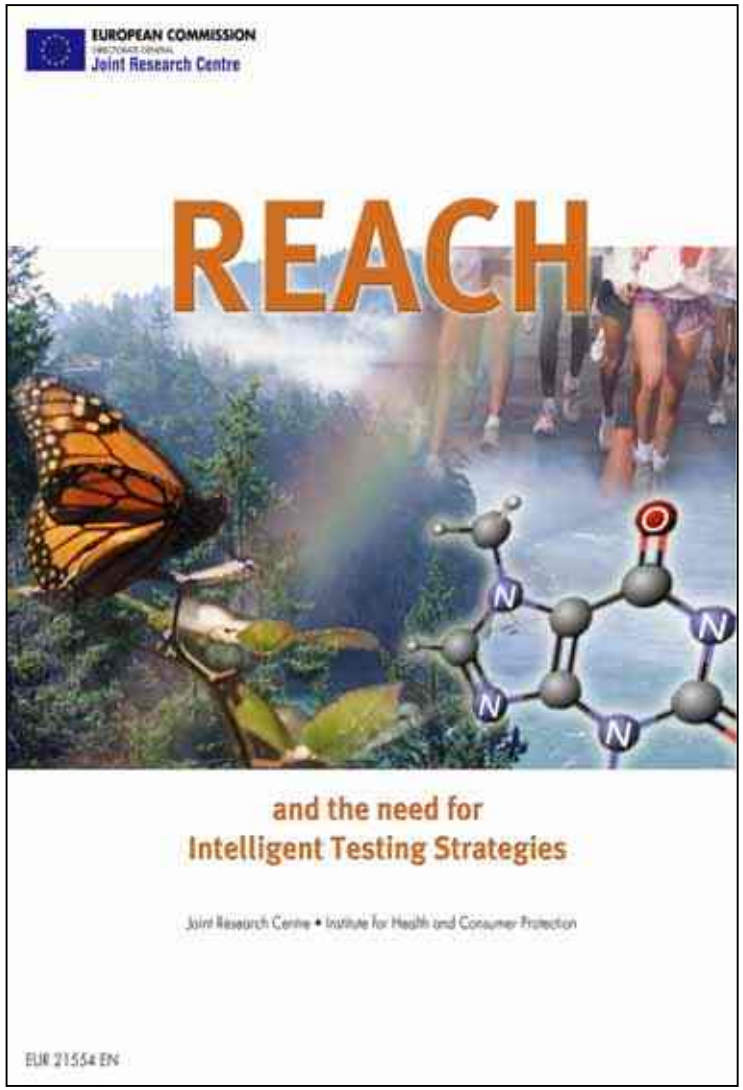
JRC report on ITS



- Report published on occasion of the 7th November conference
- Analysis of ITS needs and opportunities for REACH

Towards ITS in RIP 3.3

- Support to ECB
- Steering Group with CEFIC / ECETOC / others
- Continualtion of Stakeholder Expert Goups with MS
- Expert Nomination Process
- Continous transparence to DGs, ECB and stakeholders
- „Think tank“ ITS

ECVAM taskforce

- T. Hartung / C. Klein
- J. Riego Sintes, ECB
- L. Scott, P&G, seconded to ECVAM 2004-5
- M. Kayser, BASF
- Patric Amcoff, SAWA/OECD

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How we like to spell REACH after introduction of ITS

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

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