



EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre



Joint Research Centre

Introduction to ECVAM and status of 3R methods in Europe

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ihcp



ECVAM Mission

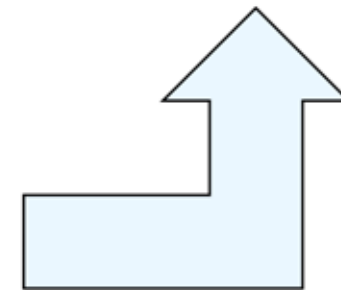
Directive 86/609/EEC



- Validation
- Database
- Research
- Communication
- ESAC

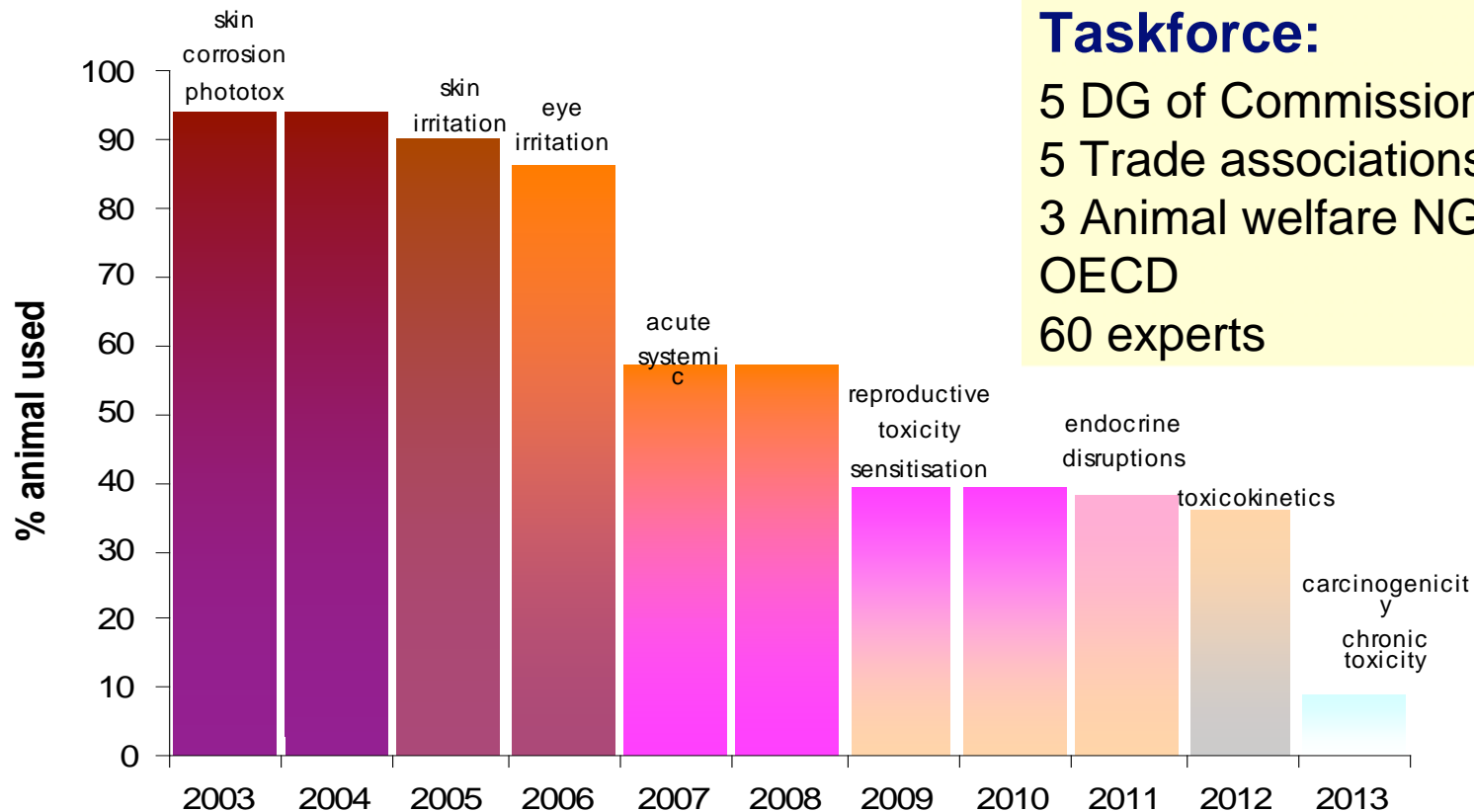


ECVAM
Reorganisation



7th amendment to the cosmetics directive

Joint Research Centre



Taskforce:

- 5 DG of Commission
- 5 Trade associations
- 3 Animal welfare NGOs
- OECD
- 60 experts



Stop finished products
& ECVAM-validated alternatives



Deadlines ingredients





REACH

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

Medical Research Council UK, 2001:

⇒ **Financial cost:** 9 billion €

⇒ **Cost of animal life:** 13 million

⇒ **Timescale:**

⇒ for 1-100 t: 2048

⇒ for 100-1000 t: 2024

⇒ for 1000+ t: 2018

Lower figures in DG ENTR and JRC/ECB studies (2003)



**billions of Euro, millions of animals,
decades of testing**



The ECVAM Business Plan

- **A ten year program to meet the expectations from legislation**
- **Bundling of all stakeholder activities**
- **Combination of strategic and technical developments**
- **Estimated costs for test optimisation and (pre-) validation of 150 M€**
- **Adoptation of ECVAM's services already initiated**



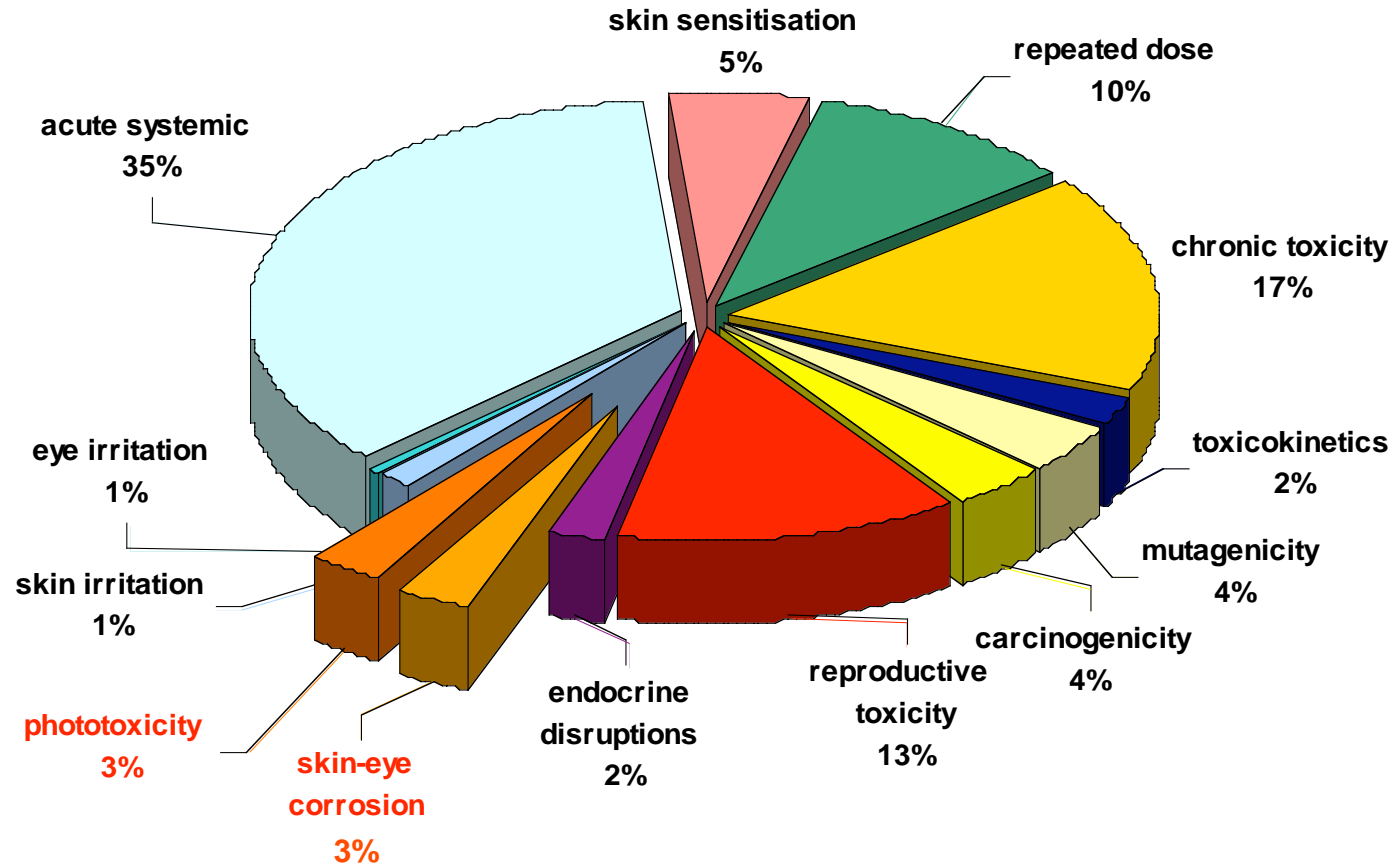
Reorganisation

KEY AREAS

- Systemic toxicity
- Topical toxicity
- Sensitisation
- Carcinogenicity
- Reproductive toxicity
- Toxicokinetics
- Ecotoxicology
- Biologicals
- SIS databases
- QSARs
- Strategic developments
(GLP, GCCP, HTS, toxicogenomics)

ECVAM staff teams
plus laboratory activities
plus external experts

Animals used in Toxicology per Year

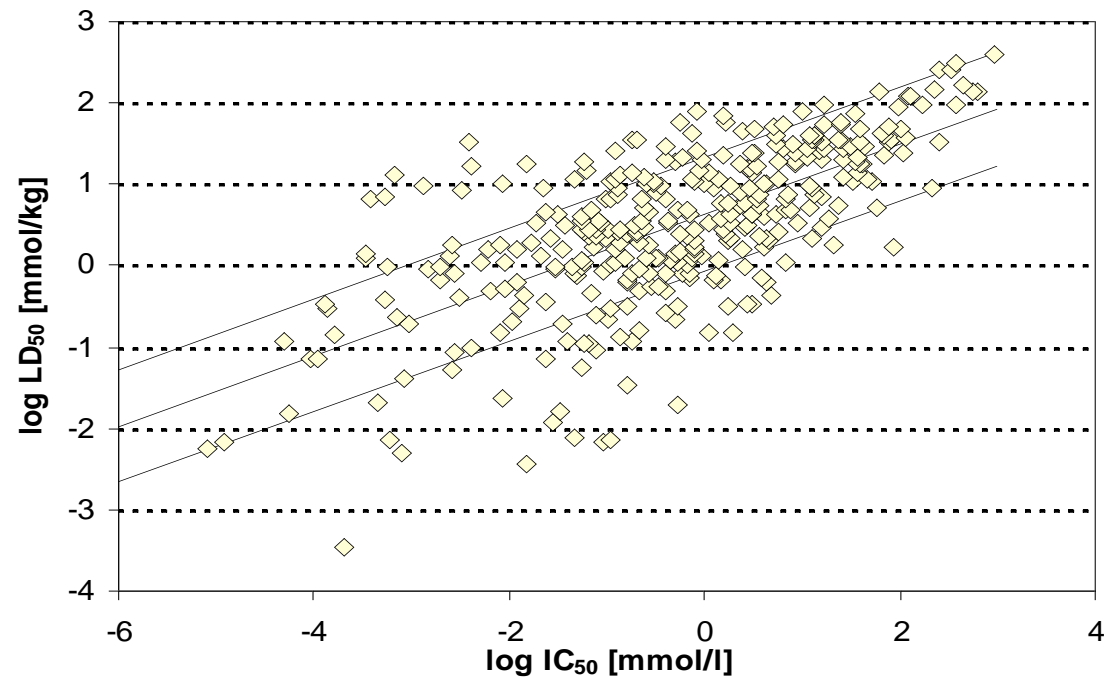
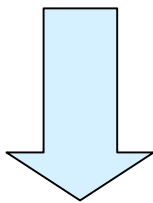


3rd Commission Report on the Number of Animal Used in the EU

Example: Acute Systemic Toxicity

ICCVAM/ECVAM Validation

Registry of
Cytotoxicity



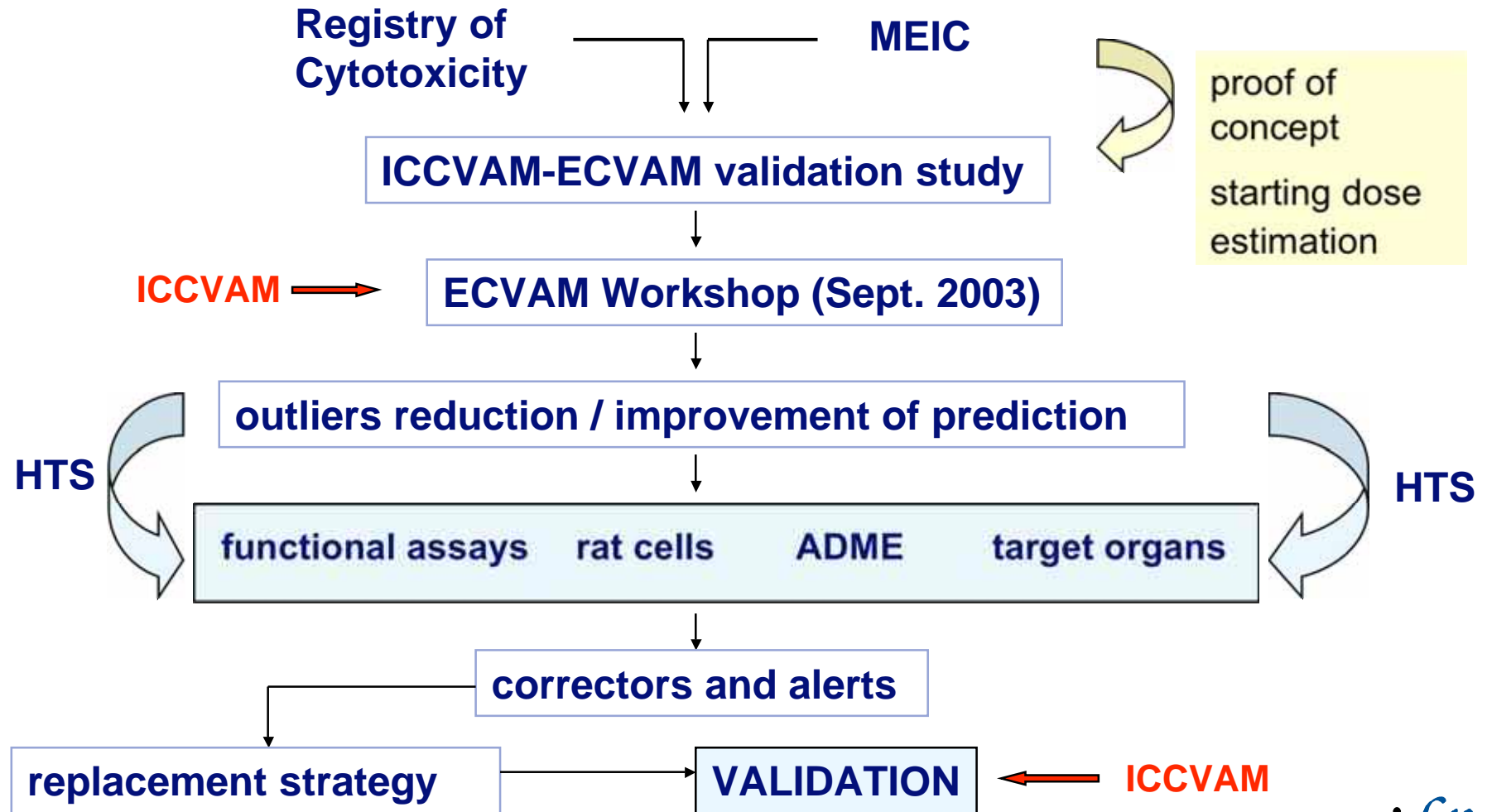
ECVAM-ICCVAM

Joint Validation Study of two

***In Vitro* Basal Cytotoxicity Assays**

Strategy to Replace Acute Toxicity Testing

Joint Research Centre





A-Cute-Tox

Granted Integrated Project (9 million €)

Joint Research Centre

Coordinator:

Dr. C. Clemedson



Steering Committee:

Dr. L. Risteli
Prof. J.V. Castell
Dr. J.A Vericat
Prof. B. Blauboer
Dr. P. Prieto



WP1: In vivo database

WP2: In vitro database

WP3: Testing strategy
Iterative amendments

WP4: New endpoints
New cell systems

WP5: Correctors - ADE

WP6: Correctors - metabolism

WP7: Correctors – target organ
7.1 Neurotoxicity
7.2 Nephrotoxicity
7.3 Hepatotoxicity

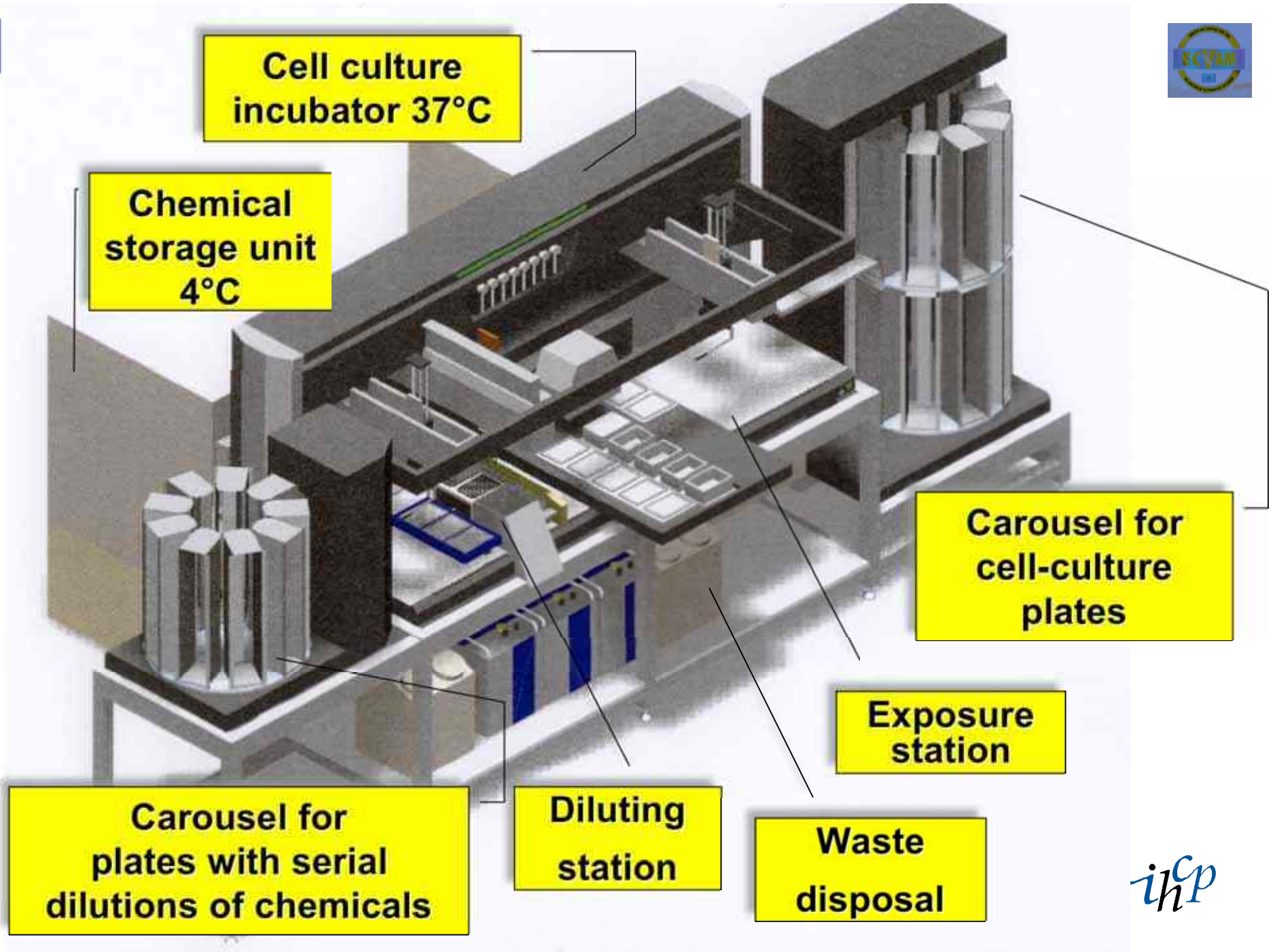
WP8: Technical optimisation of
the test strategy

WP9: Prevalidation

WP10: Management, dissemination
and exploitation of results

- 37 participants
- 14 States
- 17 Universities
- 10 SME
- 4 Research Institutes
- 2 Industries
- 2 Foundations
- JRC

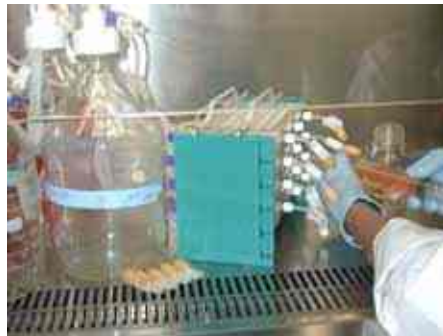






Chronic Toxicity

- Workshop on Long-Term Toxicity Testing (1999)
- Pilot study (flow-cell bioreactor, static-cell bioreactor)



- Evaluation of a new perfusion system developed in FP4
 - ongoing prevalidation
 - PREDICTOMICS
 - Workshop 2004





PREDICTOMICS

Coordinator:

Prof. Jose V. Castell



Executive board:

Prof. Jose V. Castell

Prof. Walter Pfaller

**Dr. Bernt Garthoff
(ECOPA)**

**Prof. Thomas Hartung
(ECVAM)**



WP1: Liver cell model developments

- Innovated 3D culture technology
- Hepatocyte cell differentiation
- Stem cell technology

WP2: Kidney cell system developments

- Primary cultures, mono- and co-cultures
- New perfusion culture techniques
- Molecular biology studies on kidney differentiation

WP3: Optimisation of analysis tools

- Genomics
- Proteomics
- Cytomics

WP4: Mechanistically based gene markers identification (liver)

- Exposure to model toxicants
- Analysis of effects related to the mechanisms of toxicity
- Identification of marker genes

WP5: Mechanisms of nephrotoxicity and identification of toxicity markers

- Exposure to toxins and co-factors
- Analysis of activated genes
- Identification of mechanistically relevant marker genes and novel endpoints

WP6: Database generation. Analysis of model predictivity. Prevalidation

- 14 participants**
- 8 States**
- 6 Universities**
- 2 SME**
- 4 Industries**
- 1 Foundation**
- JRC**



Reproductive Toxicology

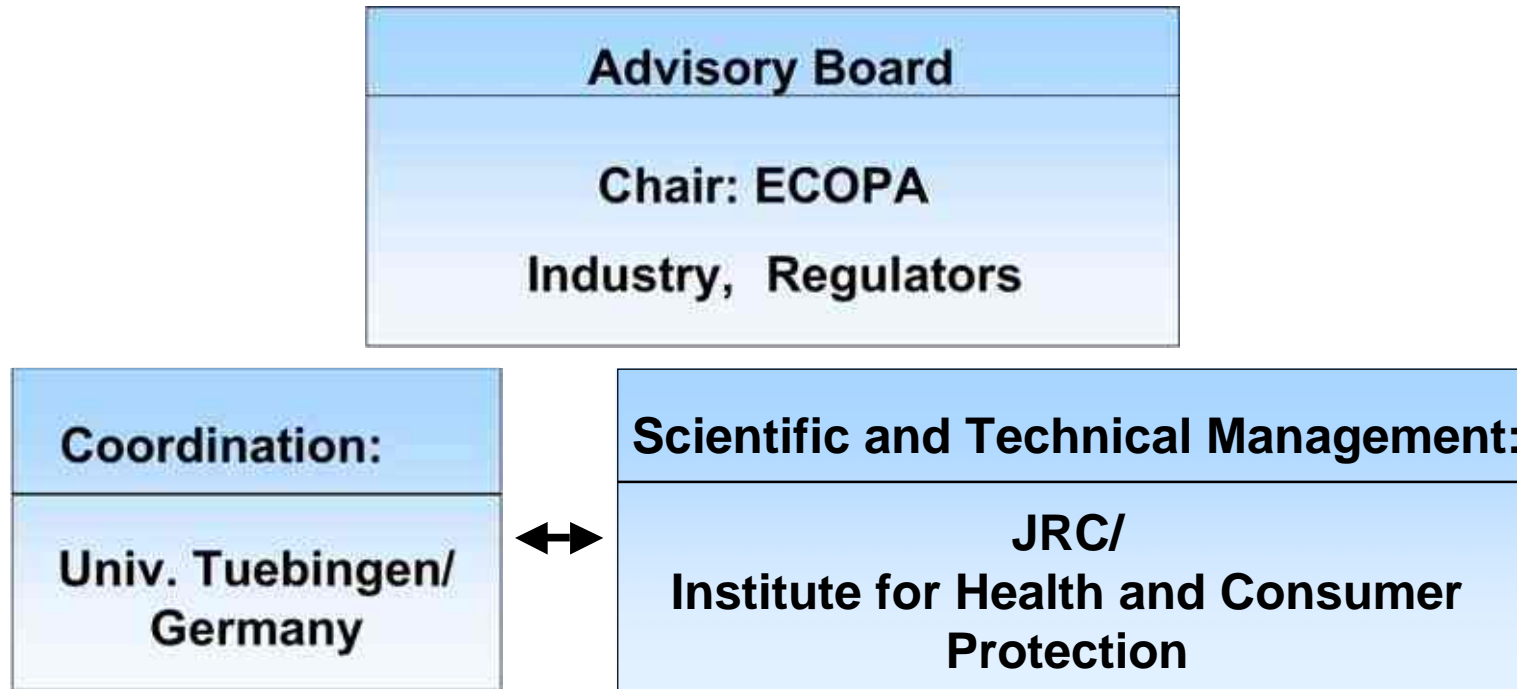


**Integrated project
(35 partners, granted 9 M€)
Coordinators:
Uni Tübingen / ECVAM**

Management of the ReProTect



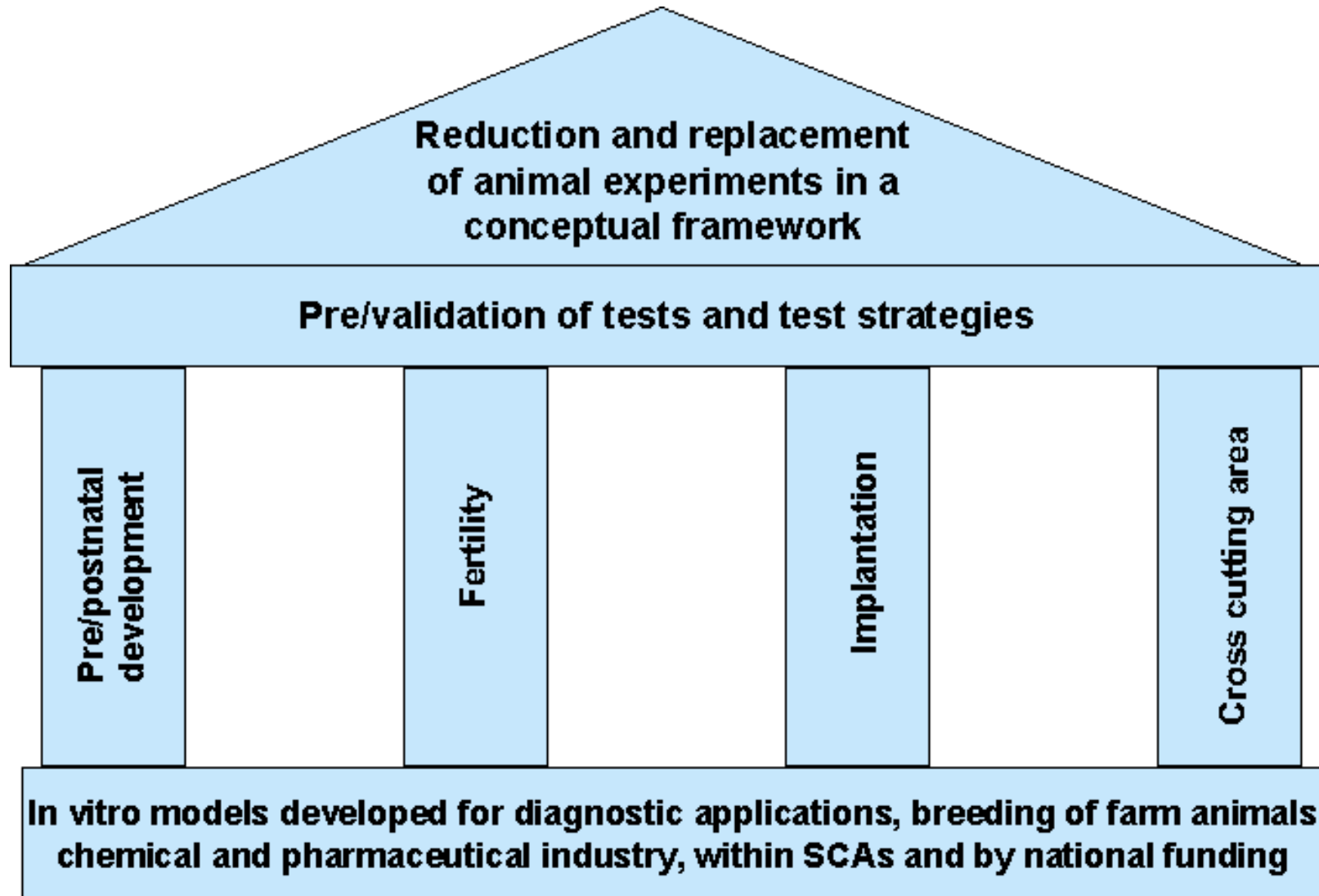
Joint Research Centre



Science	Technology	Strategy	Exploitation
Fertility	QSAR	Conference	Training
Prenatal	Array technology	Workshops	Train the trainer
development	Sensor technology	Task forces	e-learning
Implantation	Biometry	Regulators	
		Industry	



Structure of the ReProTect



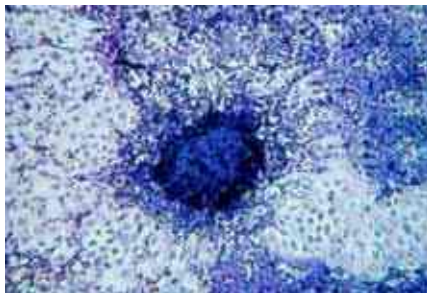


Carcinogenicity

(Animal test: 1 M€)

Focus on non-genotoxic agents

Establishment of
Cell Transformation Assay



2004:
(Pre)validation

2003:
Toxicogenomics
(Pilot study,
Workshop)





Actions key area carcinogenicity
1st taskforce meeting 1'04

Micronucleus Test

Workshop 4'04

Cell Transformation

Workshop 4'04

**Genomics Pilot Project
with Bayer &
Affymetrix**

completed



(Quantitative) Structure-Activity Relationships

January 2003: New JRC Action in collaboration with ECB, OECD

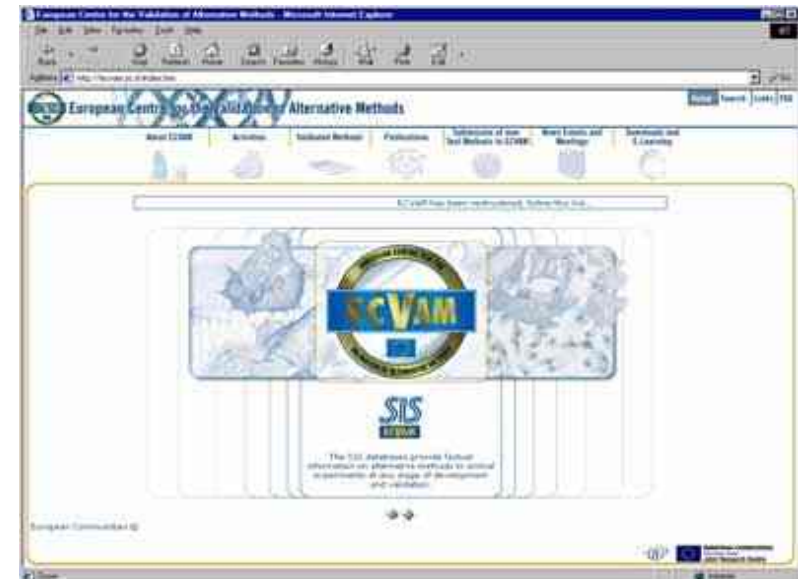
- promoting the development
- validation
- promoting the regulatory acceptance



March 2003: ECVAM & ECB hosted
1st OECD Expert meeting on (Q)SARs

The ECVAM Scientific Information Service (SIS)

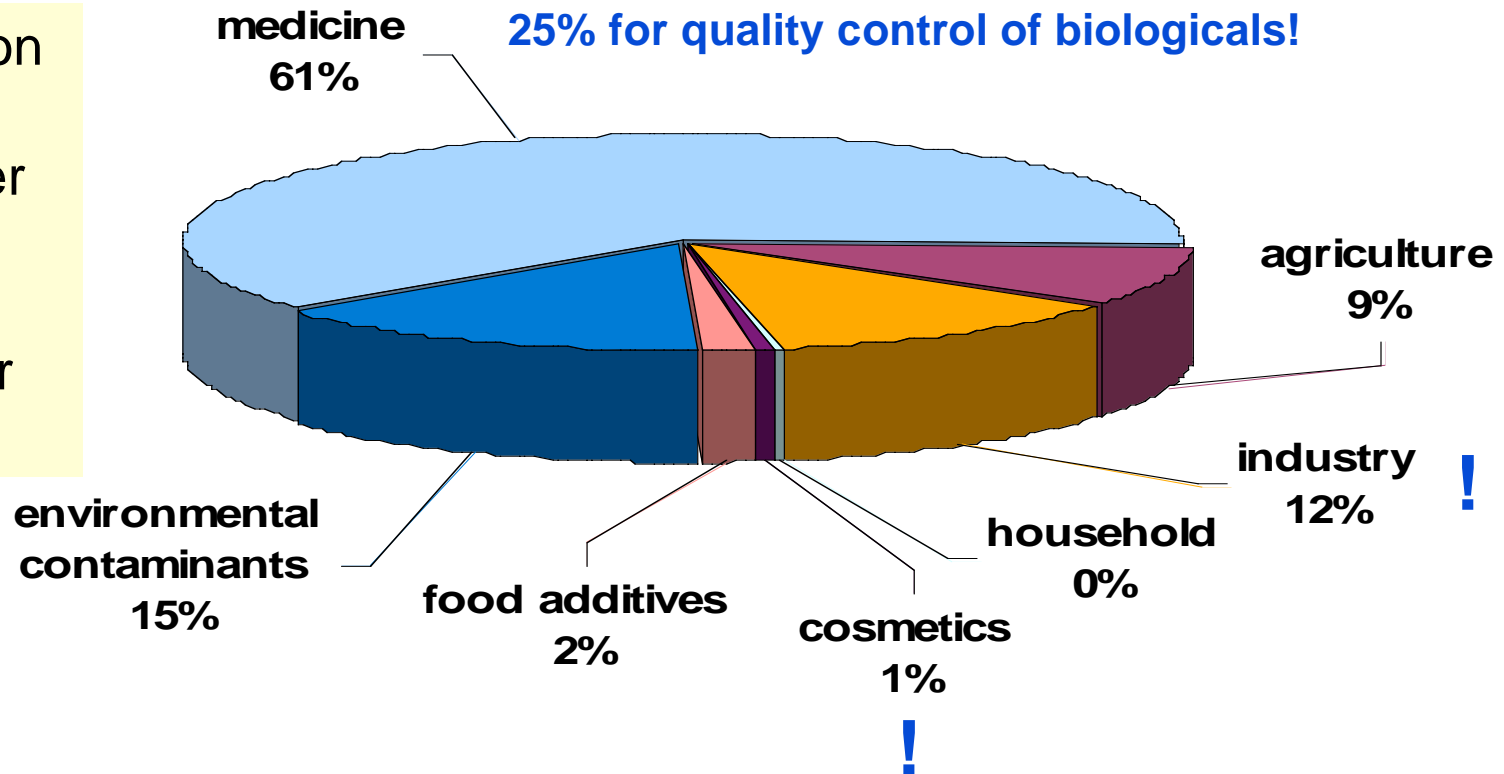
- Full public availability of the SIS databases
- ECVAM Thesaurus on Advanced and Alternative Methods (TAAM)
- Extension of the ECVAM web site
- Extension to in silico
- E-learning





Animals used in Toxicological or other Safety Evaluations

10 million animals used per year in the 15 member states

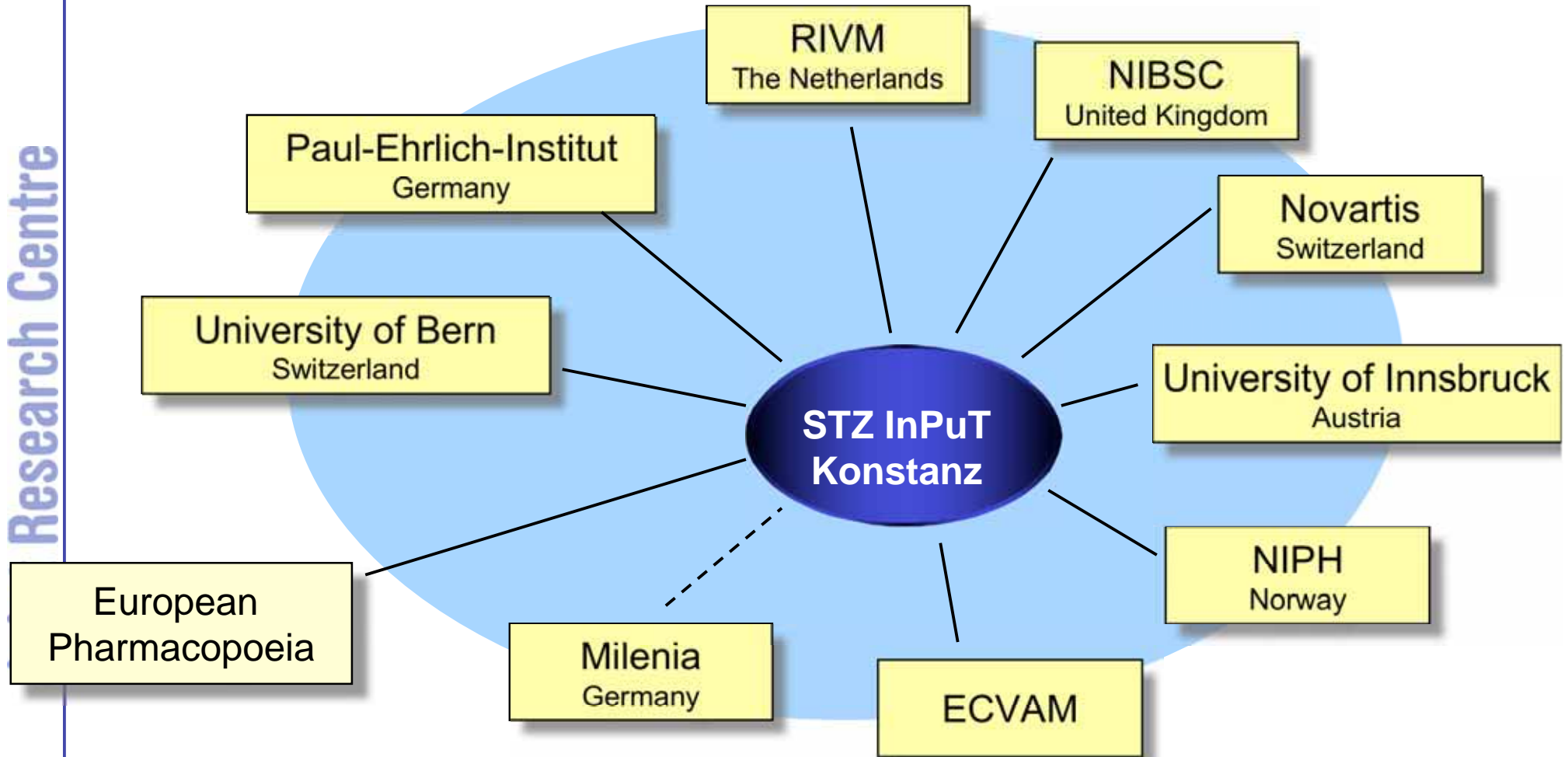


3rd Commission Report on the Number of Animal Used in the EU



Completed Pyrogen Test Validation

Research Centre



Results of the Pyrogen Test Validation – Press Conference 5'03



Compared to the rabbit test, all tests are:

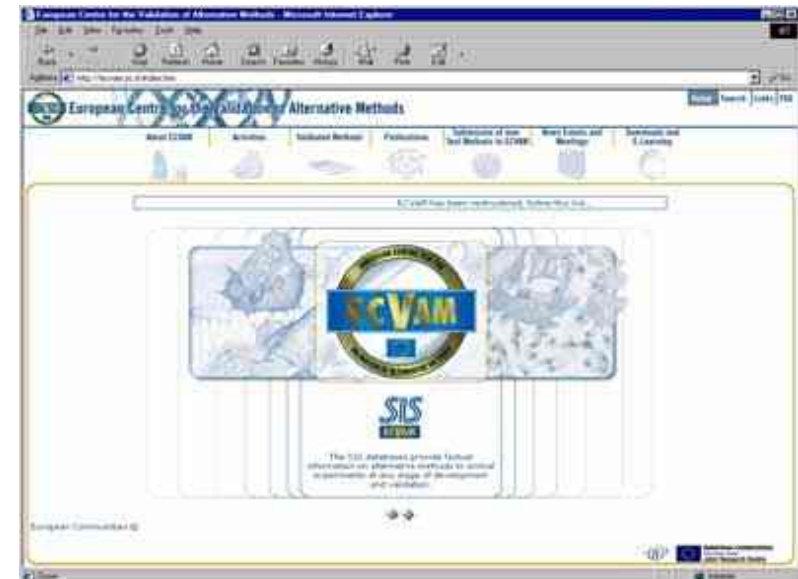
- more sensitive
- better reproducible
- less costly
- quantitative
- quicker

Alternatives can outperform in vivo:

- more standardized
- state-of-the-art technology and mechanistic understanding
- based on human cells
- high throughput allowing replicate tests
- lower costs

The ECVAM Scientific Information Service (SIS)

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ECVAM Workshop Reports

1999

Eye irritation
Polyclonal antibodies
Non-invasive methods for cosmetics
GLP
Skin irritation
Carcinogenicity

2000

Biomarkers
Avian vaccines
Phototoxicity

2001

Pyrogen tests
Human tissue bank
Long-term toxicity
Intestinal barriers

2003

Ecotoxicology
Rabies vaccines
Acute systemic toxicity
Embryotoxicity
Validation of toxicogenomics
Blood brain barrier

N° participants: > 200

N° countries: > 20

N° in publication/preparation 7





Main results: Regulatory Acceptance

METHODS	67/548/EEC	OECD	Ph.Eur.
Phototoxicity	2000	2002	
Skin corrosion (2)	2000	2002	
Percutaneous absorption		2002	
Deletion of LD ₅₀	2001	2001	
Skin sensitisation		2002	
Erysipelas vaccines			2003
Tetanus vaccines (2)			2003



What you can expect from ECVAM

- **Coaching of the development of alternatives, not the development itself**
- **(Pre-)Validation in international collaborative studies**
- **Support for regulatory acceptance**
- **International harmonization**



What ECVAM expects from industry

- **Making available:**
 - in vivo data
 - reference chemicals
 - promising in-house test methods
- **(Resources for the) development of alternatives**



*Nothing is as strong as an idea
whose time has come.*

Victor Hugo