



ECVAM update at the end of framework programme 7 (2003-2007)

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ECVAM

- Animal welfare directive 1986 (86/609/EEC)
- Established 1991
- 16 methods validated until 2002
- Business plan and reorganisation 2003 responding to 7th amendment of the cosmetic directive 2003 emerging REACH legislation 2007
- 9 methods validated 2006
- 63 staff members
- Reorganisation 2007 (more drug, vaccine, food, nanotox plus CORRELATE)
- Expansion building 2007-2008

Cosmetics industry and the 7th amendment



- EU: 2.000 companies, 60 billion € turnover
- EU: 5.000 new products per year, 25% turnover with products released within last 6 months
- Marketing ban if testing finished products or not using ECVAM-validated methods since 2003
- Phasing out ingredient testing with test and marketing bans in 2009 and 2013

Chemical industry and REACH



- EU: 27.000 companies (96% SME), 590 billion € turnover = 33% of world market, 1,7 million employees
- EU: occupational skin disease cost 3 million work days per year, i.e. about 600 million €
- 86% of toxicological data on 'old' chemicals are lacking
- REACH will assess 30.000 chemicals marketed >1 ton/year
- Expected 180.000 preregistrations 2009
- Expected 70% of testing 2011-2017

Reach is coming...but how beautiful will it be?



- Possible finalisation with 2nd reading on 13th December
- 2003: ECVAM business plan:
 - cut animal numbers by 50%
 - about 50 validated tests required, i.e. 150 in validation
- 2005: ECVAM responsible for coordination test strategy development
- Additional impact of "suitable" methods

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REACH ANNEX XI

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

1.4. In vitro methods

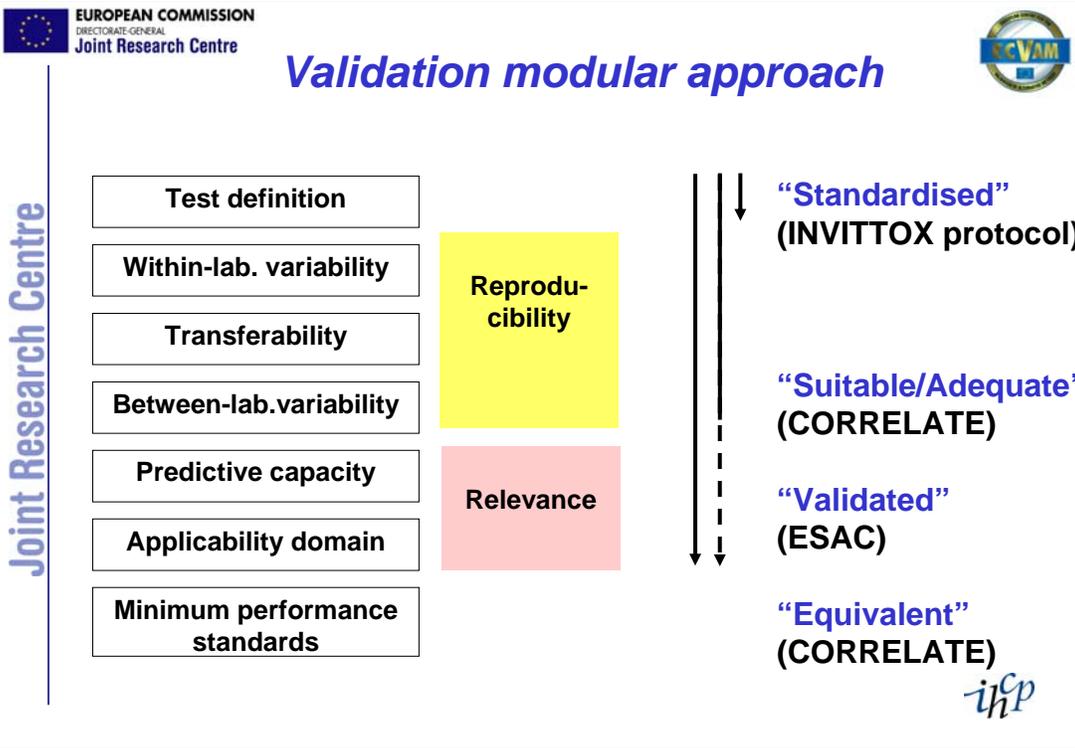
Results obtained from suitable *in vitro* methods may indicate the presence of a certain dangerous property or may be important in relation to a mechanistic understanding, which may be important for the assessment. In this context, "suitable" means sufficiently well developed according to internationally 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.

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Joint Research Centre

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Topical toxicity

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- Skin corrosion accepted OECD 2004, 3rd model validated 2006, 4th expected 2007
- Skin irritation replacement under ESAC review, expected 2007, me-too developments waiting
- Refinement for eye test under ESAC review, expected 2007
- 10 alternative for eye test under validation (8 retro- and 2 prospective), expected 2008

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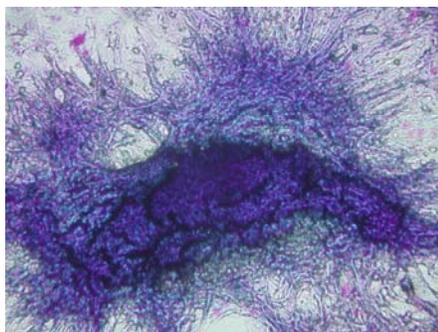
Systemic toxicity



- ECVAM/NICEATM study to predict starting dose by cytotox under review, human toxicity better predicted than by animal
- Prediction of non-toxic chemicals (70%) by cytotox under validation, expected 2008
- tiered test for dermal and inhalation
- A-Cute-Tox, expected 2009



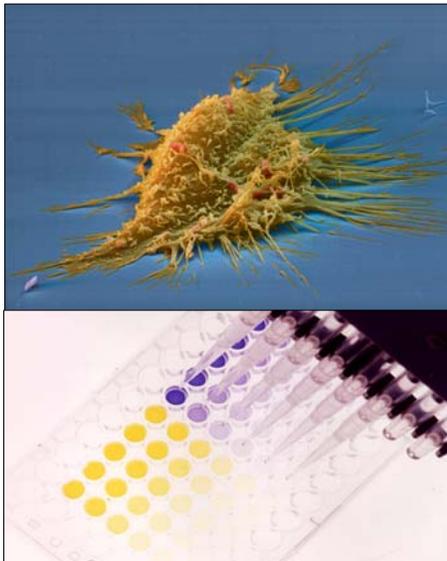
Mutagenicity / Cancer



- 2 Cell transformation assays under validation, expected 2008, OECD TG in parallel
- Micronucleus validated 2006
- COMET assay under validation (lead JaCVAM)
- validation skin models for genotox
- Workshop false-positives, follow-up studies with COLIPA
- omission pos. control, peer-review prepared



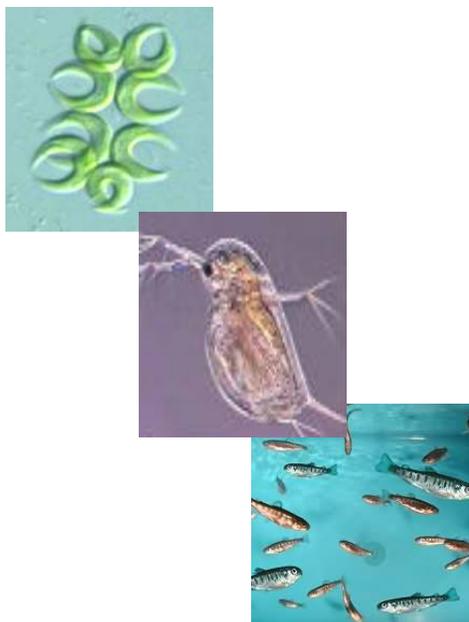
Sensitisation



- LLNA cut down approach under validation, expected 2007
- Three replacements to start validation 2007
- Non-radioactive LLNA under validation
- Sen-it-i.v.

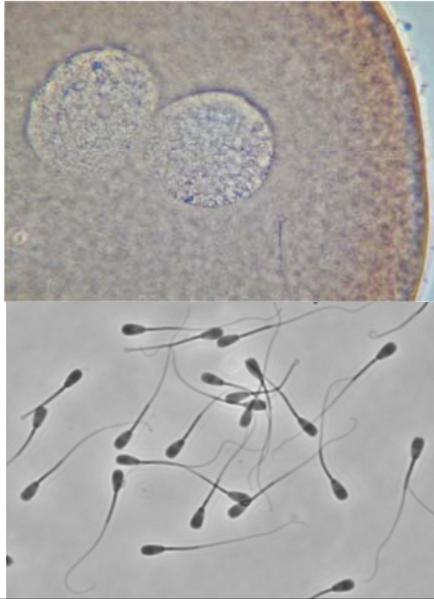


Ecotoxicology



- Test strategy acute ecotox validated 2006
- Fish egg/embryo test prepared for peer-review, expected 2007
- Planned validation bioaccumulation with ILSI/HESI

Reproductive toxicity



- Validated embryotoxicity tests to substitute for 2nd species and priority setting
- (extended) one-generation study under validation, expected 2008
- test battery for alerts under validation
- 11 endocrine disrupter tests under validation, expected 2008
- ReProTect



Problem Reproductive Toxicity

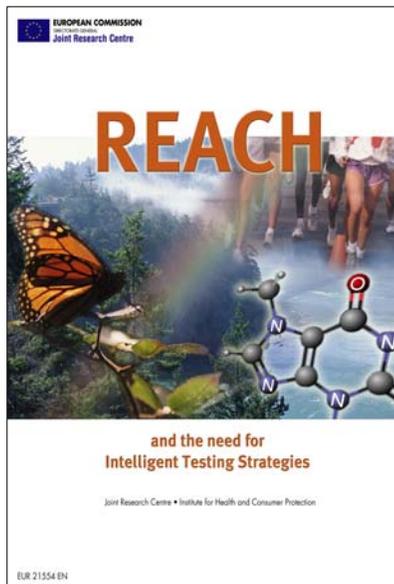
- Dominant test demand: 80% of animal use in REACH (12 million) for 5.500 substances
 - Lacking capacities and experience (e.g. only 70 two-gen-studies in 25 years)
 - Limited predictive value (60-70% between species)
 - High proportion of false-positive results
- ➔ REACH could lead to many follow-up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



Calculation consequences of reprotox studies for 1000 chemicals (assuming 5% prevalence, 60% inter-species correlation)

	5%	60%		
Human		1 st spec.	2 nd spec.	Total
50 +	↙ ↘	30 + 20 f-	↙ ↘	42 + 8 f-
950 -	↙ ↘	380 f+ 570 -	↙ ↘	608 f+ 342 -

Test strategy development in RIP 3.3

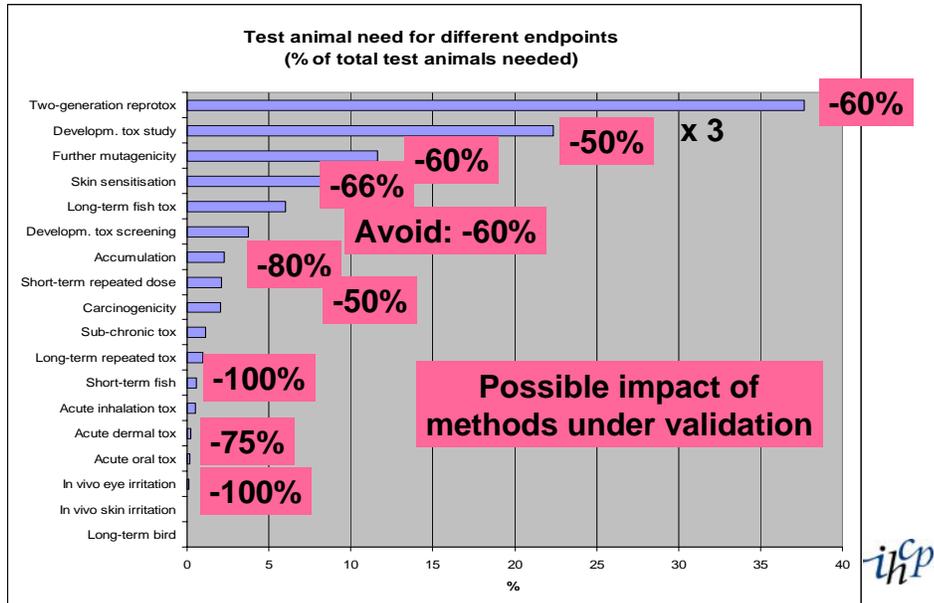


- CEFIC management, strong regulator involvement, >200 experts
- ECVAM coordinated for COM, 28 staff members involved
- About 2.000 pages ready 4'2007
- Methods under validation already foreseen
- Avoided (so far) as standard requirements: neurodevelopmental tox., endocrine disruption, respiratory irritation and sensitisation, 2nd species for two-gen study

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



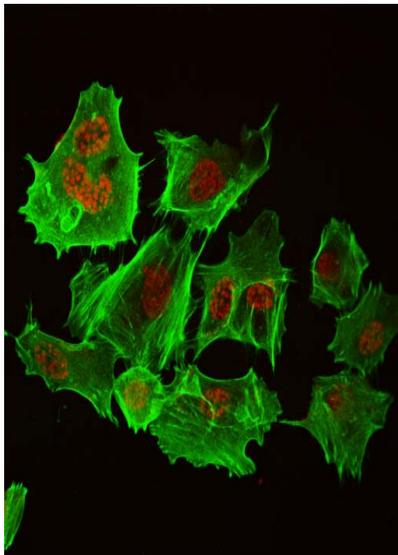
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Reassessment animal numbers REACH



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- Testing of 29.200 (1-10 tons), 5.000 (10-100 tons), 2500 (100-1.000 tons) and 2.700 (>1.000 tons)
- 38 million animals if all tests are carried out
- Expected 10% existing data and 33% waiving of testing: 23 million animals
- Impact read-across, chemical classes and (Q)SAR: 18 million animals
- Impact replacement and reduction methods: 8 million animals

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State of the play...

- 13 research projects with 264 partners (80 million €)
- 160 methods under validation
- Expected 100 methods "suitable" for REACH
- Currently 125 INVITTOX protocols
- 9 methods validated in 2006
- Expected 40 methods validated until 2009
- Impact analysis (peer-reviewed 7'2006) suggests 50% animal reduction by alternatives plus 20% by (Q)SAR
- Draft testing strategies in RIP 3.3 ready to be finalised by 4'2007



ECVAM DATABASE SERVICE
ON ALTERNATIVE METHODS TO
ANIMAL EXPERIMENTATION

Current Activities & Prospects

- Online availability of the whole DB-ALM data contents as an Oracle based database service (29th October 2006)
- Data collections on Reproductive Toxicity and Eye Irritation (>2 years)
- Extension of DB-ALM to include information on computational toxicology including QSARs
- ECVAM website, INVITTOX protocols, EBT platform

Toward an evidence-based toxicology

- Toxicology requires a critical review of its toolbox
- Validation is first of all a mean of quality control, which needs to be combined with quality assurance (GLP in vitro, GCCP) and structured reviews/meta-analysis
- Acceptance of novel approaches requires to understand the limitations of the current ones
- Article: S. Hoffmann & T. Hartung „Toward an evidence-based toxicology“ Human and Experimental Toxicology 2006, 25:497-513

Next steps:

Current development of an internet platform

Conference in fall 2007



Europe goes alternative **2nd Conference, Brussels, 18th of December 2006**



- Hosted again by Commissioners G. Verheugen (DG ENTR) and J. Potocnik (DG JRC / DG RTD)
- **European Partnership** (7 trade associations, 22+ companies)
- Action programme published
- Mirror group established
- Various workshops

