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Joint Research Centre

REACH and current alternative methodological approaches in (pre)validation

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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 validatio
- Additional impact of "suitabl methods
- 2005: ECVAM responsible fo coordination test strategy development

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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Validation modular approach

- Test definition
- Within-lab. variability
- Transferability
- Between-lab.variability
- Predictive capacity
- Applicability domain
- Minimum performance standards

Reproducibility

Relevance

"Standardised"
(INVITTOX protoc

"Suitable/Adequa
(CORRELATE)

"Validated"
(ESAC)

"Equivalent"
(CORRELATE)

Topical toxicity

- 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 prospesctive), expected 2008

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Systemic toxicity

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

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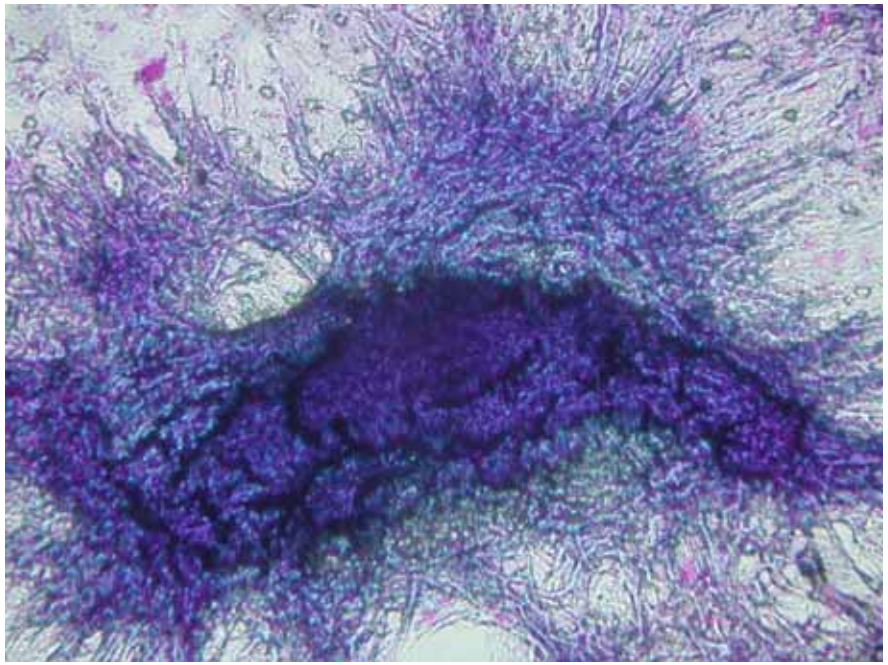
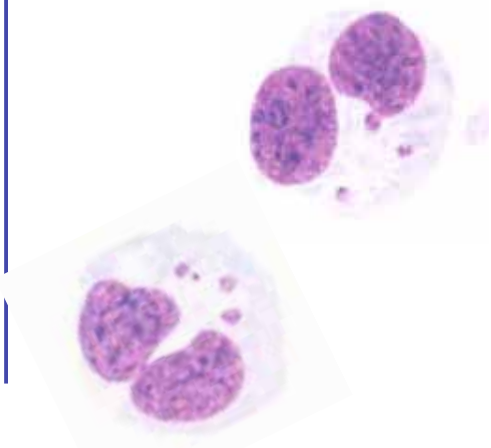
Mutagenicity / Cancer





CarcinoGenomics

- 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 genoto
- Workshop false-positives, follow-up studies with COLIPA
- omission pos. control, peer-review prepared

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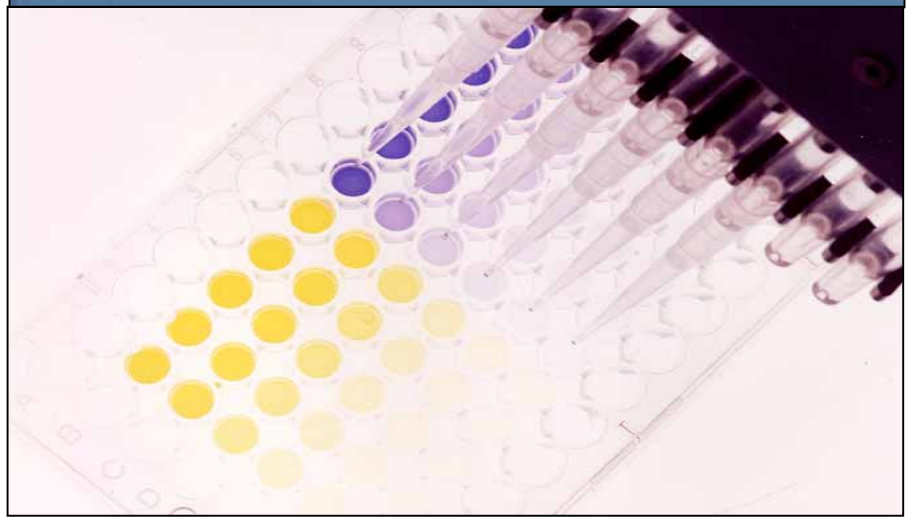
Sensitisation



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

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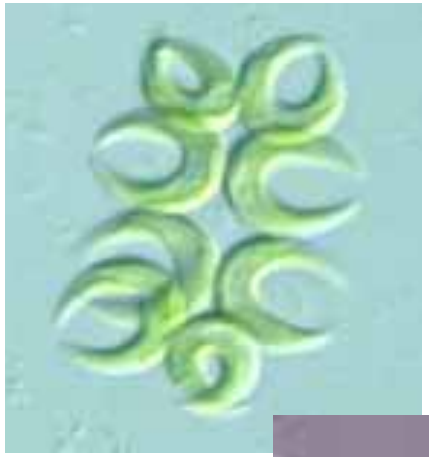
Ecotoxicology



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

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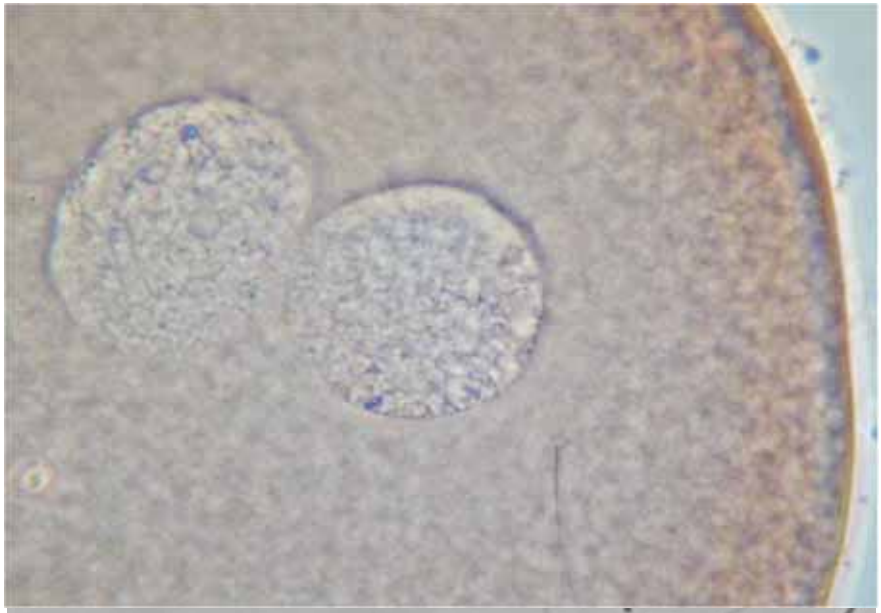
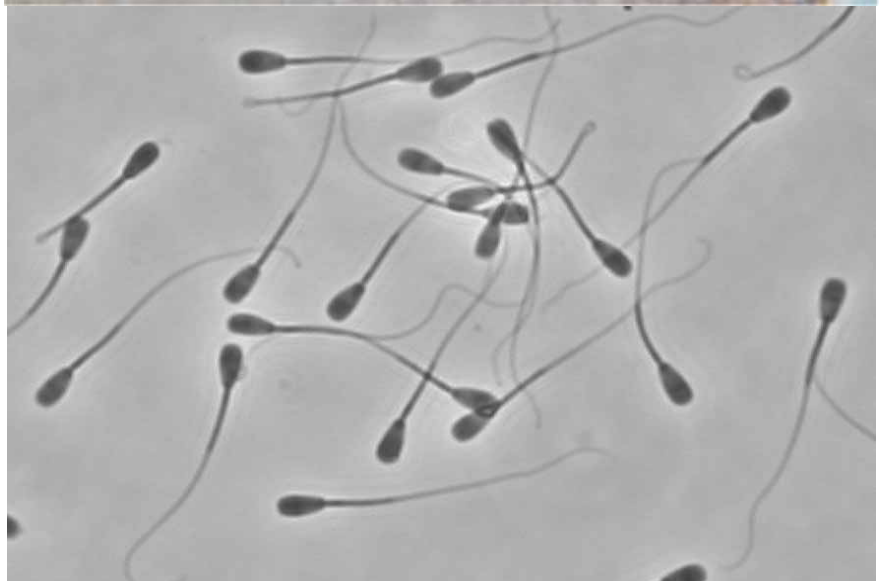
Reproductive toxicity





- 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

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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 predictve 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		**1st spec.**	**2nd spec.**	**Total**
50 +	→	**30 +**	**12 +**	**42 +**
	→	**20 f-**	**8 f-**	**8 f-**
950 -	→	**380 f+**	**228 f+**	**608 f+**
	→	**570 -**	**342 -**	**342 -**

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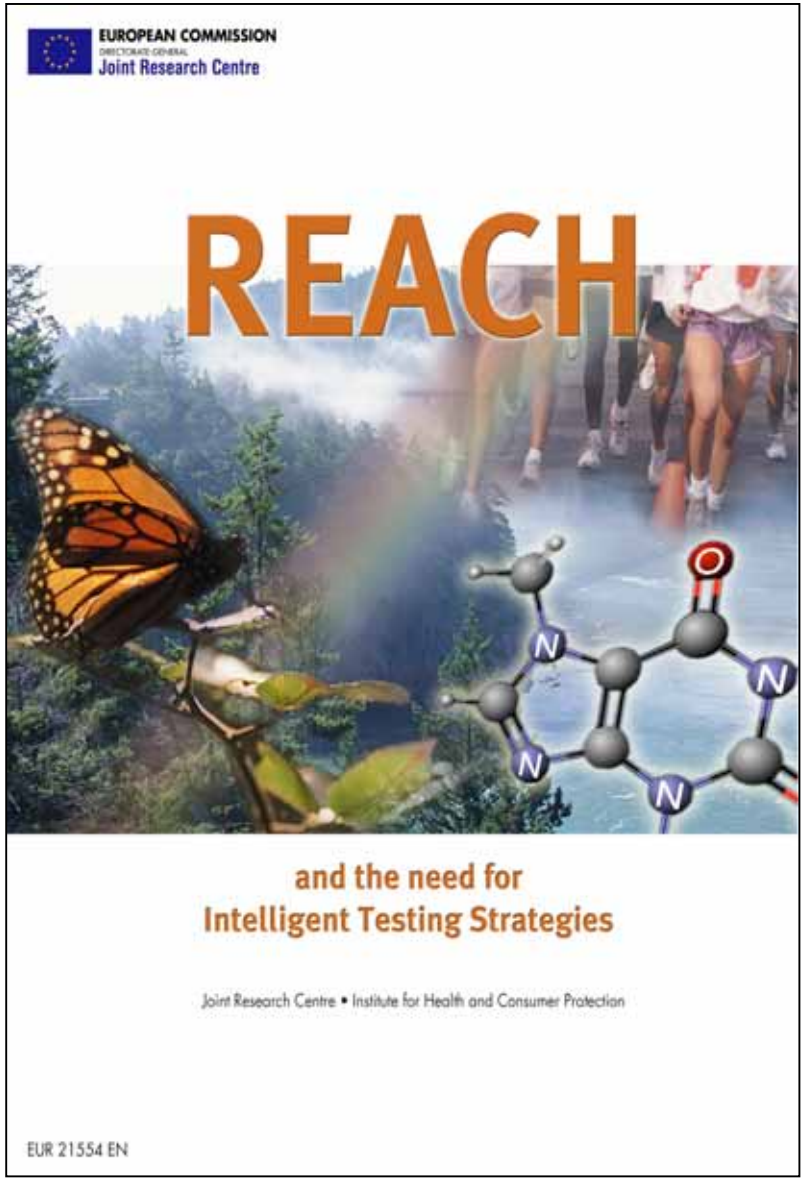
Test strategy development in RIP 3.3



- 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

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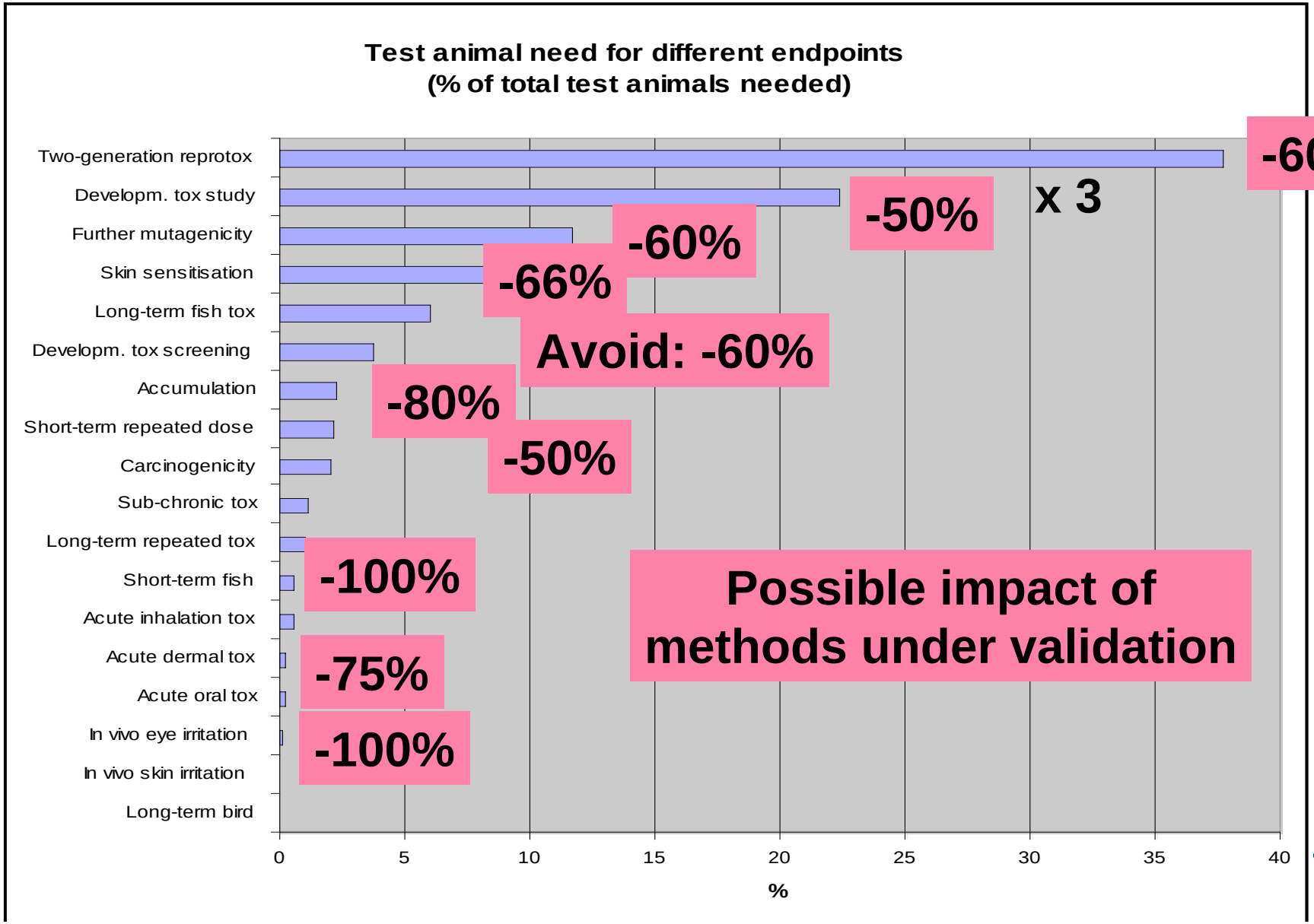
Estimated test animal need for the different endpoints (van der Jagt et al., 2004)



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State of the play…

- 13 research projects with 232 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