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ECVAM update

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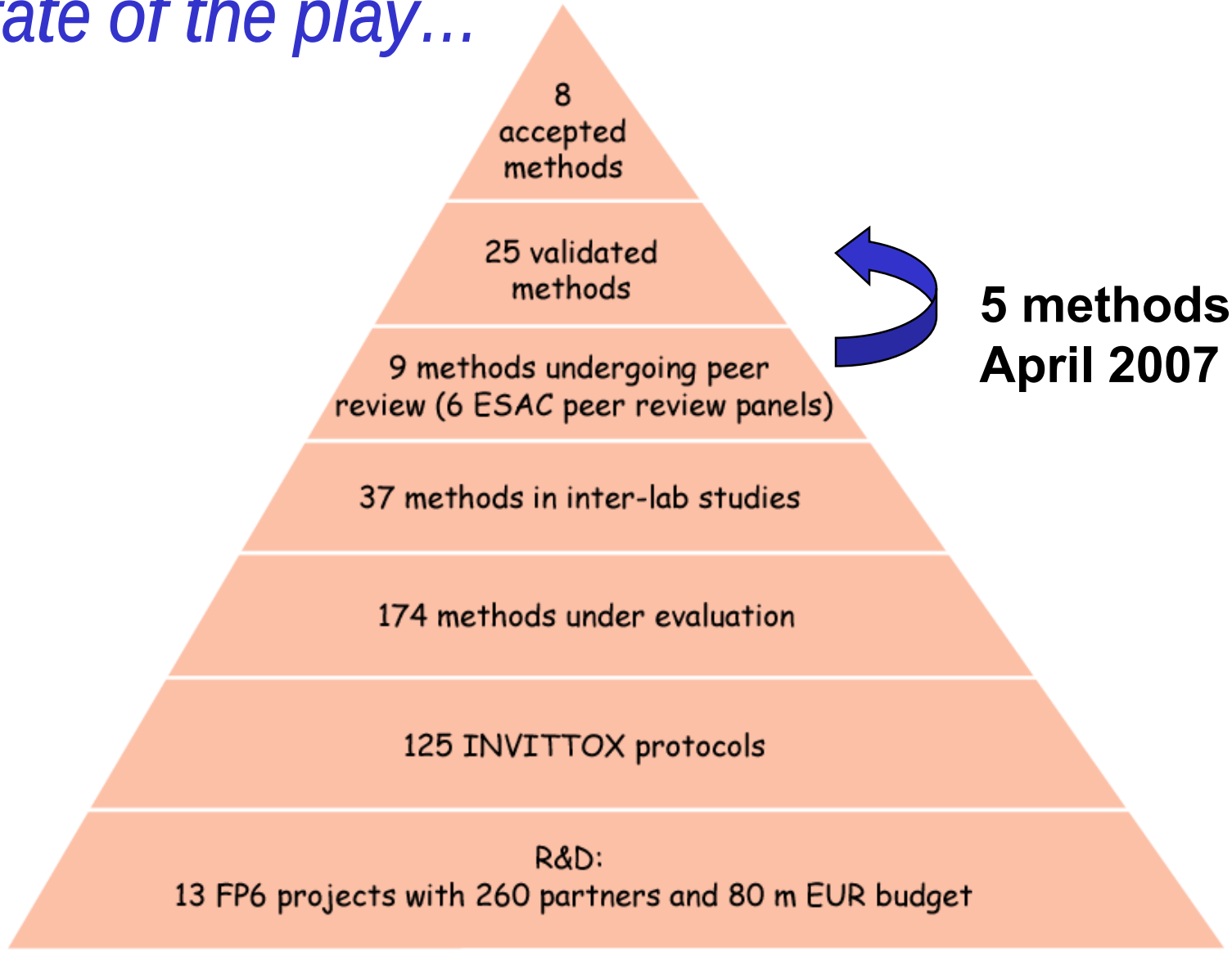
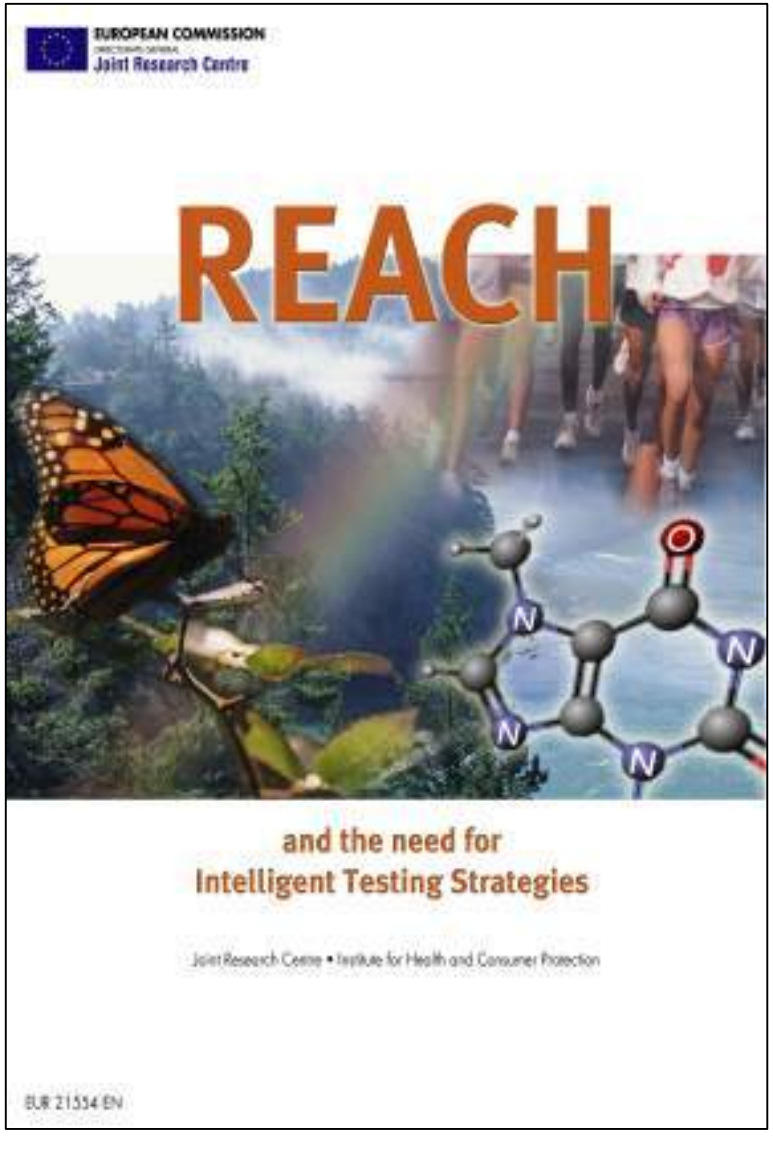
ihcp

State of the play…



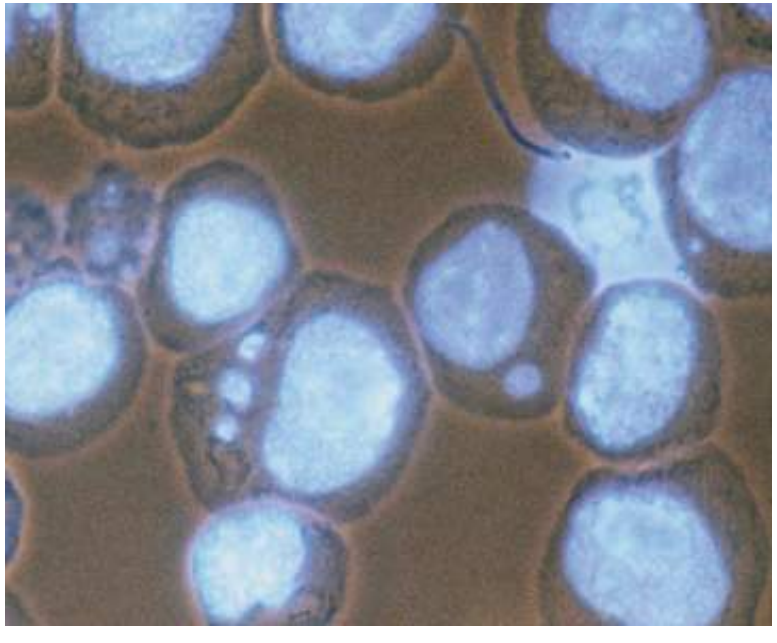
5 methods
April 2007

Test strategy development for REACH



- Key contribution to REACH implementation process
- CEFIC management, strong regulator and industry involvement, >200 experts
- ECVAM as coordinator for Commission
- About 2.000 pages ready May 2007
- Many methods under validation already foreseen

Validated 2006: Mutagenicity



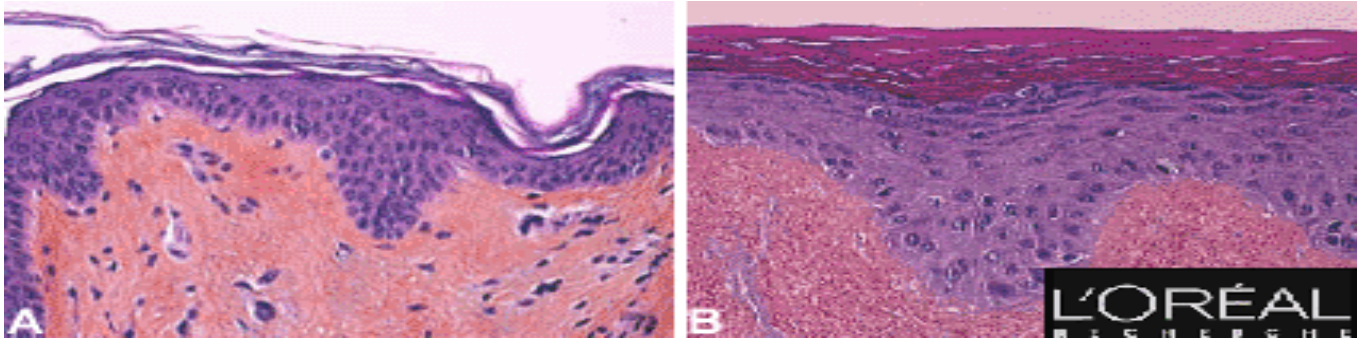
- Micronucleus test improves in vitro assessment for mutagenicity / genotoxicity
- First validation based only on a compilation of existing data, no new study
- Completed in two years, within one month included in REACH legislation
- Currently considered by OECD and ICH (International Conference on Harmonisation)
- Accelerated validation

Validated 2007: Skin irritation

- Rabbit test for drugs, chemicals and cosmetics introduced 60 years ago
- Validation study 2003-2006 of three models with 9 labs (2 U.S.), 58 test chemicals
- Best model (Episkin), optimized in an FP4 DG RTD contract, represents a full replacement

Artificial human skin

- Biotechnology product originally to treat burn patients
- 5 European and 1 American producer
- Forerunner Episkin opens the avenue for others to follow
- 2009 deadline of cosmetics directive, 10.000 REACH substances



Skin

Reconstructed epidermis EPISKIN

Participating laboratories

EPISKIN	EPIDERM	SIFT
L'Oréal (F)	ZEBET (D)	Syngenta (UK)
Unilever (UK)	Institute for In Vitro Sciences (USA)	DuPont (USA)
Sanofi-Synthélabo (F)	BASF (D)	TNO (NL)

Chemicals Selection

Source	R38 (Skin irritants)		Non irritants		Totals
	GHS Irritants	GHS Mild Irritants	GHS Mild Irritants	GHS Non Irritants	
The New Chemicals Database (NCD)	7	9	3	14	33
ECETOC	5	2	2	10	19
TSCA	1	1	0	4	6
Totals	**25**		**33**		**58**

NCD chemicals: Obtained thanks to the collaboration with ***25 suppliers*** that agreed to disclose chemical identities

ECETOC and TSCA: ***Commercially available*** chemicals

Final selected chemicals

- Balanced distribution across EU and GHS categories
- Balanced distribution of Draize scores
- Solids and liquids represented in EU and GHS categories
- Sensitisers and non-sensitisers
- Irritants and non-irritants to the eye
- Pure substances and multi-component mixtures
- Broad coverage of physicochemical ranges

Examples	**log Kow**	**- 3.5 to 11.5**
	water solubility	**10^{-3} to 10^{+6} mg/l**
	vap. pressure	**10^{-6} to 4.10^{+3} Pa at 20-25^{0}C**

Overall Predictive capacity of the methods

EPISKIN (MTT)	**SENSITIVITY:**	**77.6%**
	SPECIFICITY:	**80.7%**
EPISKIN (MTT + IL 1α)	**SENSITIVITY:**	**90.7%**
	SPECIFICITY:	**78.8%**
EPIDERM (MTT)	**SENSITIVITY:**	**60.1%**
	SPECIFICITY:	**88.8%**

Validated 2007: Eye irritation

- Retrospective evaluation with U.S. ICCVAM
- 4 tests analyzed, 2 qualify for the detection of severe eye irritants confirming an ECVAM analysis of 2003
- 8 other assays and the suitability for mild irritants currently under evaluation
- Intense collaboration with COLIPA
- REACH 10.000 substances; critical for cosmetics 2009

Validated 2007: Skin allergy

- OECD accepted, validated alternative method (Local Lymphnode Assay) is the reference method for 30.000 REACH chemicals
- Test strategy to test only highest dose results in 50% less animals with <1% of substances missed
- Concept by ECVAM task force 2006
- Foreseen already in REACH test strategy (saves 240 thousand mice)

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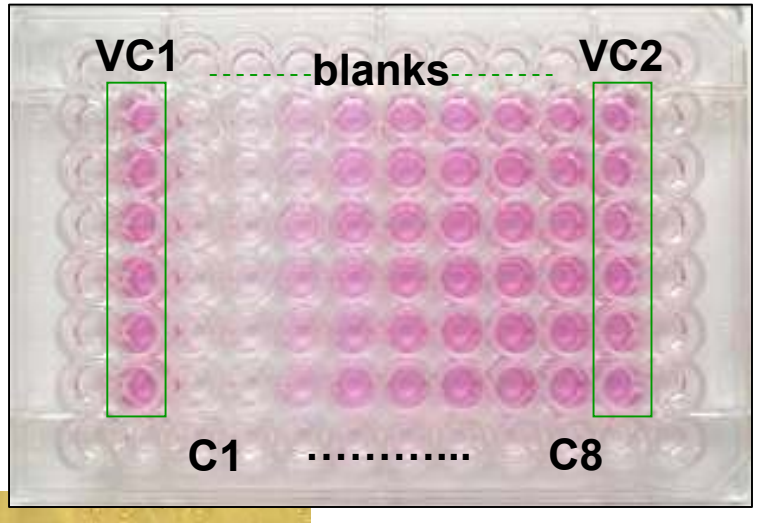
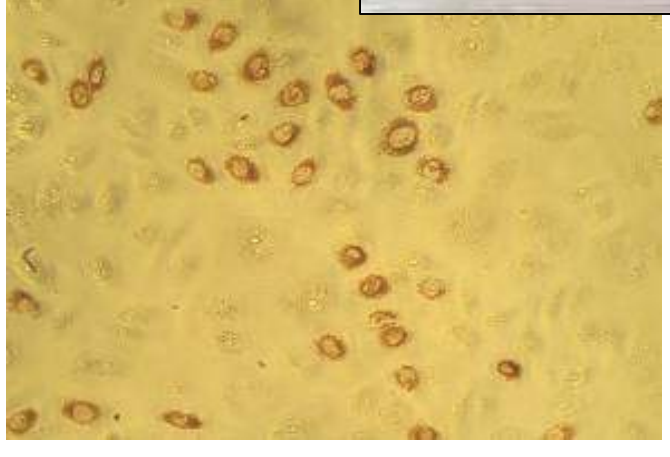
*The 3T3/NRU cytotoxicity assay**

- **NRU cytotoxicity assay is a cell survival/viability chemosensitivity test.**
- **Lysosomes of viable cells bind NR.**
- **Distinguish between viable, damaged and dead cells.**
- **NR absorption measured at optical density 540 ± 10 nm.**

Plate layout



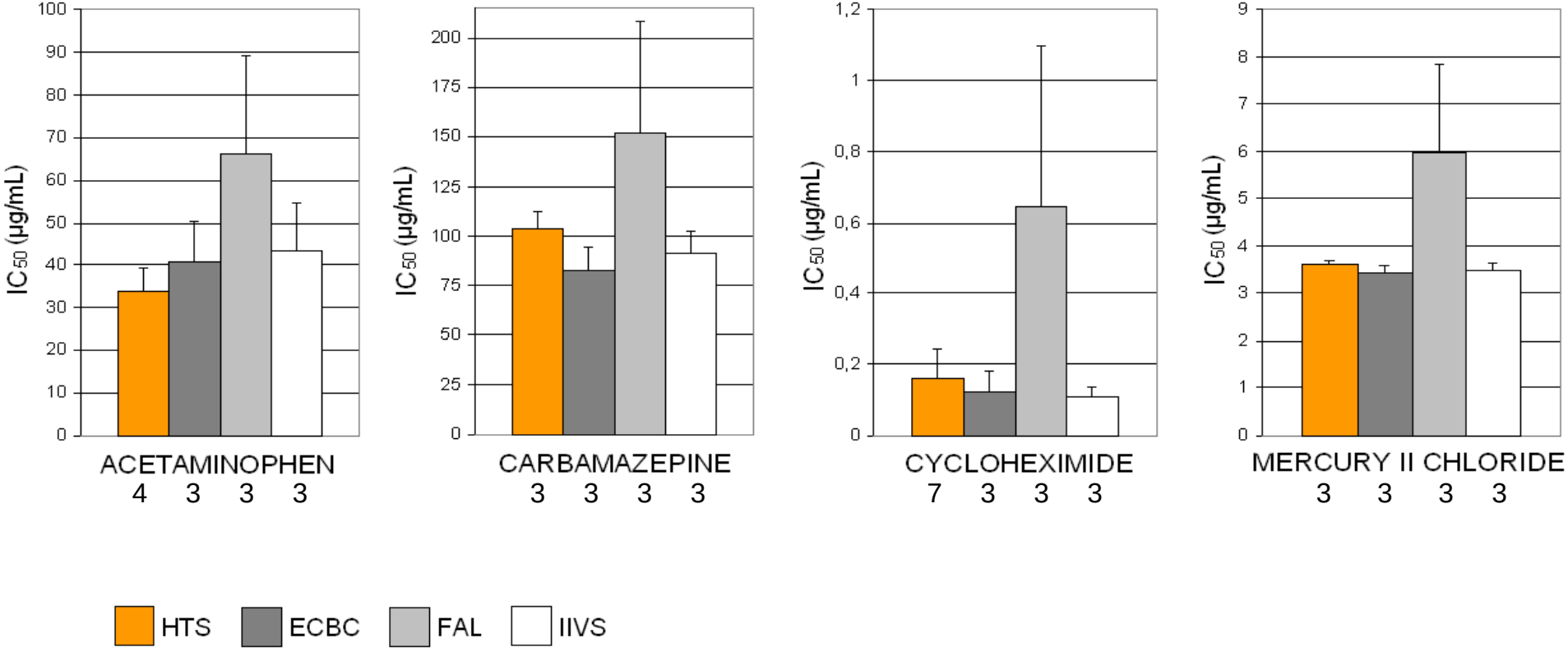
8 concentrations, 6 replicates



Cells incorporating supravital NR dye

***Subject of International Validation Study by NTP-NICEATM (USA) and ECVAM.**

HTS and the NICEATM/ECVAM Validation Study



Role model evidence-based medicine

Learning from experience may be nothing more than learning to make the same mistakes with increasing confidence.

Petr Skrabanek, James McCormick

Follies and Fallacies in Medicine
Tarragon Press, Glasgow, 1989

Evidence-based Toxicology

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

New concept:

"Evidence-based medicine goes in vitro!"

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

Article: S. Hoffmann & T. Hartung „Toward an evidence-based toxicology" Human and Exp. Tox. 2006, 25:497-513

What ?

- DISCUSS methodologies and problems in toxicological safety assessment
- EXPLORE the available concepts of evidence-based toxicology (EBT)
- LAUNCH an initiative for formal implementation of evidence-based assessment methods

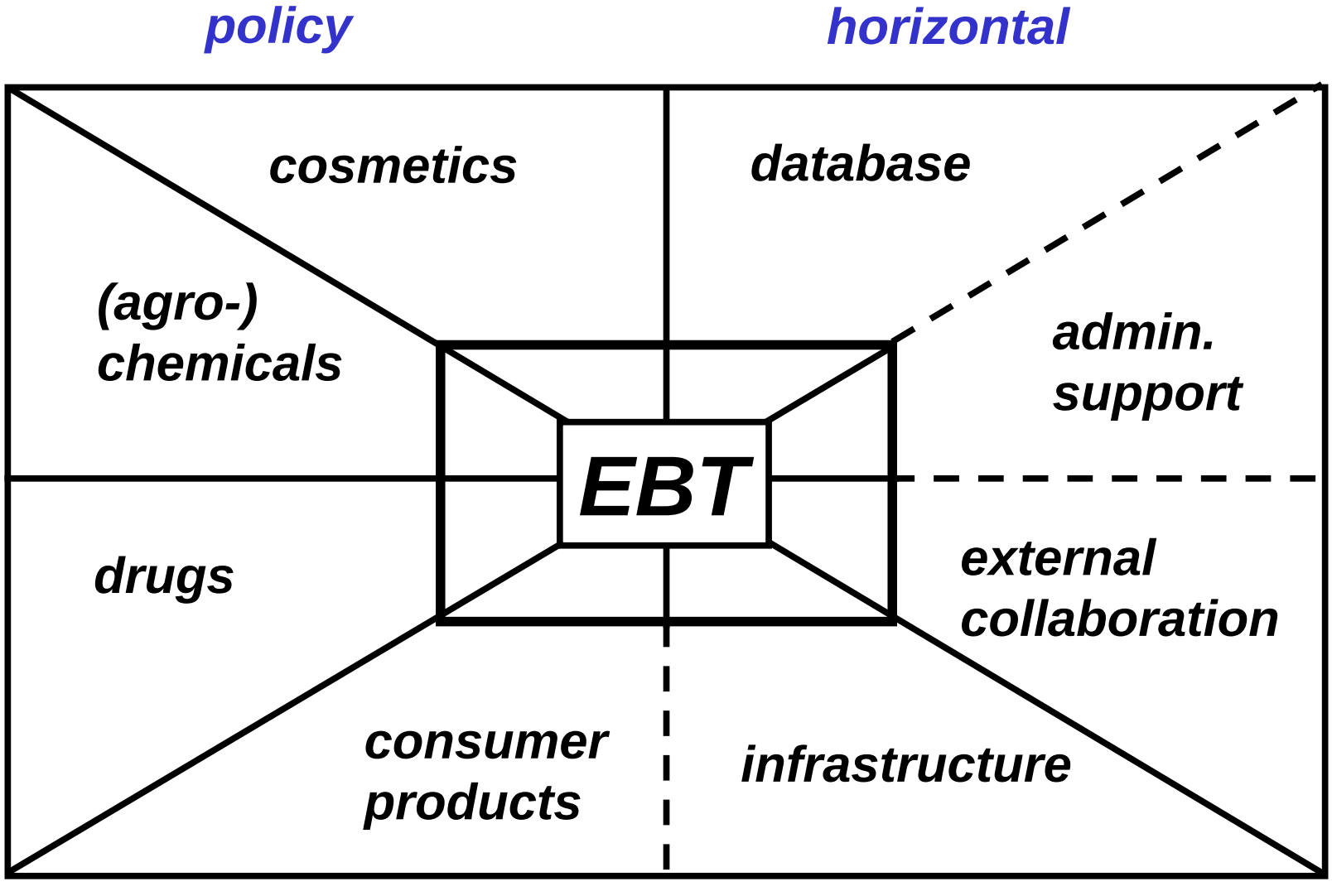
Where and when ?

- Villa Erba, Como, Italy
- October 15 to 18, 2007

How to get there ?

- http://www.ebtox.org

ECVAM structure FP7



Europe goes alternative

1st Conference, Brussels, 7th Nov 2005
2nd Conference, Brussels, 18th Dec 2006
3rd Conference, planned 5th Nov 2007

- Hosted by Commissioners G. Verheugen (DG ENTR) and J. Potočnik (DG JRC / DG RTD)
- European Partnership (7 trade associations, 27+ companies)
- Action programme


Thank you!