

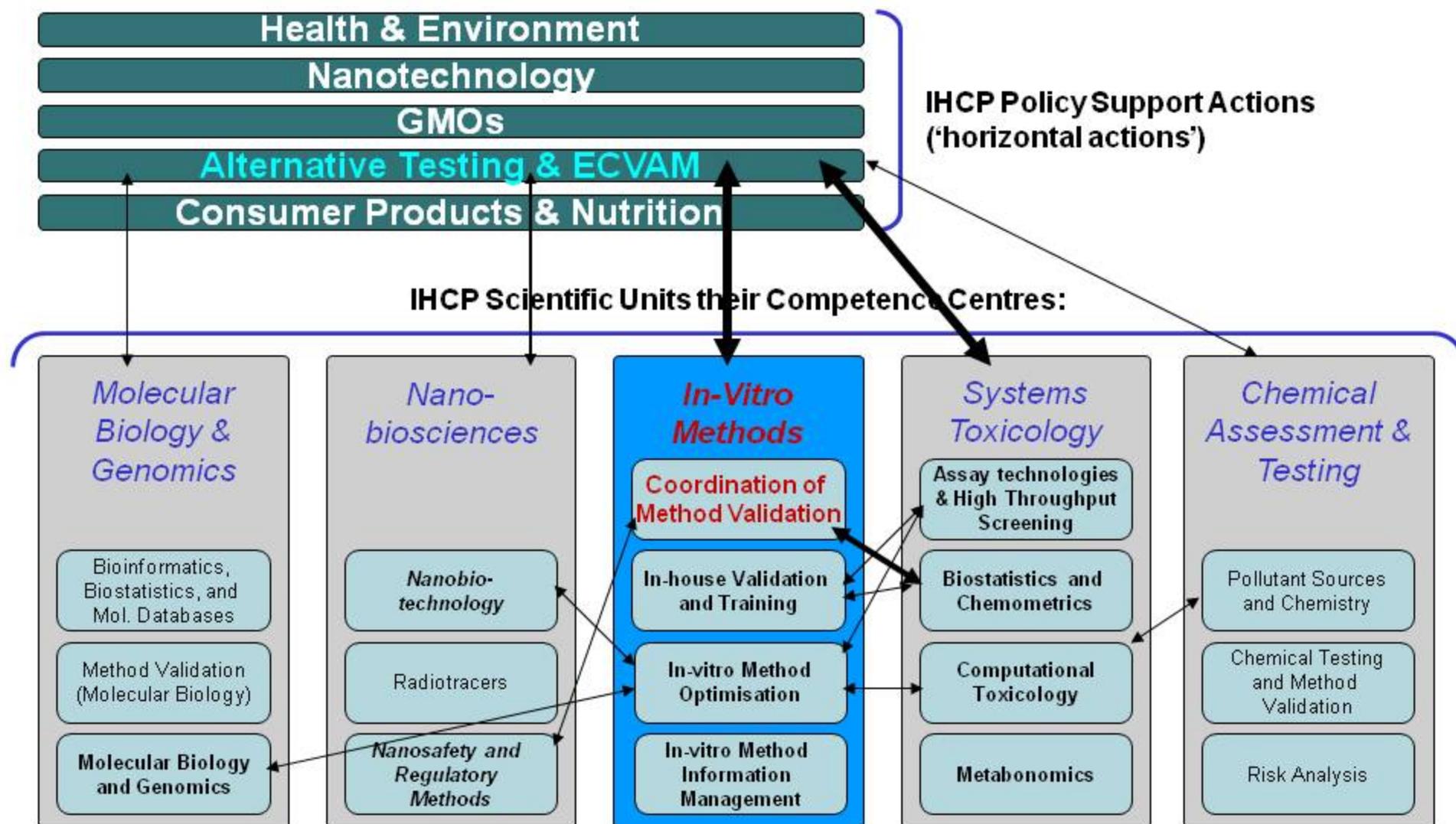
SACATAM

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ECVAM - update

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IHCP – new structure: units, policy support actions



ECVAM MISSION STATEMENT – in short

We support the EU policies in the field of Consumer protection, Environmental protection and Animal protection

by validating alternative methods for toxicology testing that implement the 3Rs and provide the same or a better basis for risk assessment and risk management as in vivo tests

and by promoting their development, their application in industry and their acceptance by regulators.

**Application in
Research ?**

Priorities

- Determined by EU legislation; e.g.
 - **REACH** (industrial chemicals)
 - animal testing = last resort – testing proposal evaluation until **Dec. 2012**
 - in-vitro method that are ready to enter validation may be used to identify hazardous properties or to measure relevant mechanistic properties
 - mechanistic information may be used in weight of evidence context
 - **Cosmetics**
 - replace all animal testing
 - Most endpoints: March 2009
 - All, incl. repeated dose and reproductive toxicity and toxicokinetics, March **2013**: marketing ban for all animal-tested cosmetic ingredients
 - **Pesticides**
 - develop within 4 years (**2013**) alternative methods for endocrine disruption testing
 - **Animal protection and welfare (86/609)**
 - minimise animal experiments and animal suffering **also in research**

Challenges & workload must be handled

- **Complex endpoints require complex test methods**

- Stimulate and support development & optimisation of ITS etc.

- **Complex test methods require complex validation**

- Streamline processes
- Develop new validation approaches

- **Complex test methods must be applied & accepted**

- Intensive dialog with test-users (industry, research(?) and data users) (regulators)
- Transparent decision making & internat. cooperation (ICATM) will support acceptance
- Training and dissemination in order to increase know how



Increasing demand for alternative methods

- **Created by EU legislation & globally increased interest**
 - Create new markets for efficient, reliable alternative tests and testing (contract labs, test systems sales, training, consultancy,)
 - more (?) test developments by research and industry
 - Officially (pre-)validated tests should have higher market value
 - more (?) test submissions to ECVAM (and other VAMs) ?
 - Closer international collaboration to address the global dimension
 - ICATM aims at sharing work and results
 - ICATM aims at speeding-up international (regulatory) acceptance

How to handle challenges & workload / 1

- **Transparent decision making during validation procedure**
 1. **Test submission:**
 - **published criteria to accept and work with developers sending in pre-submissions**
 2. **Assessment if tests meet ECVAM criteria for entering pre-validation:**
 - **formal decision needed as a positive decision would indicate a certain suitability for REACH; pre-defined criteria will be published on the web**
 - **regulatory relevance & practicality determine priority**
 3. **Decision if a pre-validated test should go into formal validation:**
 - **at that stage it is clear that a test delivers – but is it OK to go further?**
 - **regulatory relevance & practicality determine priority**
 4. **Independent peer review of validation studies:**
 - **the process should meet requirements of partner VAMs to allow sharing of outcome**
 - e.g. need to publish docs and allow for public commenting while respecting legitimate requests to protect confidential business information

How to handle challenges & workload / 2

- **Stimulate and support test development**
 - ECVAM/IHCP will continue to participate in toxicology RTD
 - ECVAM organises workshops etc. and cooperates with EPAA & others to make working in alternative toxicology attractive for scientists
 - The EU Commission provides funding for toxicological research,
 - “normal” research funding
 - a 50-million joint activity with cosmetics industry (COLIPA) addressing repeated dose toxicity
- **Stimulate test submissions for official validation**
 - Easier, stepwise submission process for ECVAM
 - Transparent decision making during validation procedure
 - Streamlined, efficient, fast, stepwise validation and (regulatory) acceptance process

State of play

GenoTox, Carcinogenicity, ReproTox

Genotoxicity:

- (pre-)validation of COMET Assay ongoing (coordinated by JaCVAM)
- Genotox assays in 3D-skin model (coordinated by COLIPA)
- Analysis of upper limits for better genotox testing strategy (disc. at ICH)
- Recommendation for reduction in genotox - *in vivo* testing (in press)

Carcinogenicity:

- Peer review of validation of three cell transformation assays (CTA) ongoing

Reprotoxicity:

- ReproTox project will yield new methods, other test submissions coming
- LumiCell validation ongoing
- Extended F1 generation study – discussion at OECD ongoing

Biologicals, Food, Ecotoxicity

Biologicals

- VICH Project with EMEA on harmonisation of requirements concerning target animal safety test for batch release of veterinary vaccines
- Organisation of the ECVAM/EPAA workshop on Consistency of Production Approach for Quality Control of Vaccines

Food

- EFSA Working Group “Welfare of experimental animals”:
 - Scientific opinion “Existing approaches incorporating replacement, reduction and refinement of animal testing: applicability in food and feed risk assessment” published in June 2009

Ecotoxicity

- Validation of in vitro trout S9 fraction assay
- OECD guidance document on The Threshold Approach for Acute Fish Toxicity Testing
- Launch of OECD Zebrafish Embryo Toxicity test validation study in April 2009 (Coordination: ECVAM)

Systemic Toxicity

Acute Toxicity:

- Balb 3T3/NRU cytotox validation study
- EPAA WG on classification aspects

Toxicokinetics, ADME, PBPK modelling:

- Growing interest to use for future test generations within ITS
- Validation studies (+ICCVAM): Human HepaRG CYP induction test method; Human Cryohep CYP induction >> test system with metabolic competence

Neurotoxicity, DNT:

- Research continues to produce results
- Collaboration with EPA on Guidance for Developing Alternative DNT-Tests
- Recent Workshop evaluated existing in vitro models, their experimental design and chemicals selection. A report is in preparation.

New Test Submissions – forthcoming validations

Skin sensitisation

DPRA
Peptide binding

hCLAT

MUSST

Received, pre-validation, phase III to start

Eye irritation

EpiOcular

SkinEthic RCE

Peptide binding

GSH

LEAN validation possible?

Eye irritation

PorCORA

Irritection Assay

Slug Mucosal Assay

Skin absorption

RhE technology skin absorption

ReproTox

VITO/B
Anti estrogenic compounds

BAYER/D

LUMICELL
(in validation)

MELM,



Knowledge management & Databanks

- **DB-ALM:**
 - Increase in registrations continues (+- 36 new users/months, Σ 1653/73 countries)
 - Online information content updating and revisions continued
- *INVITTOX* protocols:
 - remote data entry facility under development (1st quarter '09)
 - content updating priority on validated and accepted methods
- Complementary activities
 - “ECVAM Guide on good search practices”
 - Ready for editorial revision foreseen in July
 - definitive version expected 3rd quarter 2009
 - Development of on-line test submission for ECVAM
 - Portal development for the above listed ECVAM information systems

**EPAA discussion:
create
1-stop shop for all
3R related info**

The way to go: Integrated (Intelligent?) Testing Strategies

- **Starting point:**
 - ITS are the only way to achieve alternatives for complex endpoints
 - Allow integrating upcoming technologies/methods like “*omics*” (e.g. metabolomics) and non-testing approaches (computational toxicology) with *in-vitro*
 - Co-operation through ICATM should be explored
- **ECVAM will support development of ITS:**
 - ECVAM workshops, discussion *fora*; participation in other events
 - In-house research on building blocks (in vitro, in silico, in vivo(?)) and their integration
 - Participation in research projects
- **Validation of ITS:**
 - WS in November 2008 was not conclusive, ongoing discussion, next WS in autumn
 - Open questions include: which degree of validation is needed for building blocks versus complete ITS?
 - Industry is invited to present case studies, experience with non-regulatory ITS
 - Role of non-testing approaches (QSAR, systems analysis & PBPK modeling)

Some longer term challenges

*How can we validate methods (incl. ITS) that cannot be compared to generally accepted “**gold standards**” ?*

How can we convince Risk Assessors / Risk Managers to base their decisions on alternative methods?

How can alternatives get quantitative?

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Thank you for your attention !