Conferenza
NAZIONALE
BENESSERE
animale
Roma, 13-14-15 Aprile 2016

Ministero della Salute
Direzione generale della sanità animale e dei farmaci veterinari

ISTITUTO ZOOPROFILATTICO SPERIMENTALE DELLA LOMBARDIA E DELL'EMILIA-ROMAGNA

AGGIORNAMENTO E ATTIVITÀ IN ACCORDO ALLE INDICAZIONI DEL CENTRO EUROPEO DI VALIDAZIONE DEI METODI ALTERNATIVI (ECVAM)

15 aprile 2016 - Ministero della salute, Roma

Gianni Dal Negro DVM ERT RCVS

SOMMARIO

- **Metodi alternativi validati: dove trovarli?**
- **Metodi ufficialmente validati/metodi scientificamente validi**
- **Investimenti nei metodi alternativi**
- **Cosmetic Regulation (EC) No 1223/2009 e concetto di “One Toxicology”**
- **Campi applicativi dei metodi alternativi ufficialmente validati**
- **Conclusioni**

Alternatives and Replacement Research and Testing: Semantics?

- **Alternatives≠Replacement**
- **Research and Testing – Context?**

VALIDATED ALTERNATIVE METHODS

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3203912/table/T0001/

European Commission

JOINT RESEARCH CENTRE

European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM)

- Home
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- EURL ECVAM Strategy Papers
- EURL ECVAM Recommendations
- EURL ECVAM Status Reports
- Validation & regulatory acceptance
- Test Method Submission
- EU-NETVAL Validation Laboratories
- Laboratories & Research Areas
- Databases
- Glossary
- Job vacancies

EURL ECVAM's latest tweets

Tweets over "@EURL_ECVAM"

EURL_ECVAM
@EURL_ECVAM
Predicting chemicals that may cause skin allergy - validated non-animal methods do not miss chemicals requirin... bit.ly/1nfeoUs
14 days

EURL_ECVAM

The **European Union Reference Laboratory for alternatives to animal testing (EURL-ECVAM)** has been formally established in 2011, due to the increasing need for new methods to be developed and proposed for validation in the European Union. **EURL ECVAM** is hosted by the Joint Research Centre, Institute for Health and Consumer Protection (IHCP) located in Ispra, Italy.

EURL ECVAM has a long tradition in the validation of methods which reduce, refine or replace the use of animals for safety testing and efficacy/potency testing of chemicals, biologicals and vaccines. Research laboratories are able to submit to **EURL ECVAM** for scientific validation the alternative methods to animal testing that they have developed.

EURL ECVAM also promotes the development and dissemination of alternative methods and approaches, their application in industry and their acceptance by regulators.

The European Commission's involvement in activities targeted to the validation of alternative approaches to animal testing started in 1991, with the launch of **ECVAM** (the European Centre for the Validation of Alternative Methods), hosted by the **Joint Research Centre, Institute for Health and Consumer Protection (IHCP)**. As from 2011, ECVAM's tasks are assigned to **EURL ECVAM.**

The menu on the left hand side of the page helps you browse through the main content sections of the EURL ECVAM web site.

To contact EURL ECVAM, please use this interactive form.

Photo: Cell culture under sterile conditions in the EURL ECVAM microbiology laboratory. Copyright EU 2012.

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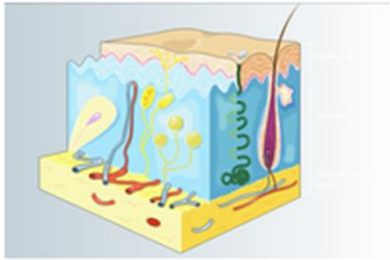
Featured article



Review of the Availability of In Vitro and In Silico Methods for Assessing Dermal Bioavailability
Read more...

Watch our video!

Our scientists show you what they are doing to advance safety assessment of chemicals without relying on animal testing

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Laboratories & Research Areas
Databases

- ChemAgora
- Chemical Lists Information System (CheLIST)
- DataBase on ALternative Methods (DB-ALM)
- Endocrine Active Substances Database
- EURL ECVAM Genotoxicity & Carcinogenicity Consolidated Database of Ames Positive Chemicals
- JRC QSAR Model Database
- Search Guide
- Tracking System on Alternative Methods (TSAR)

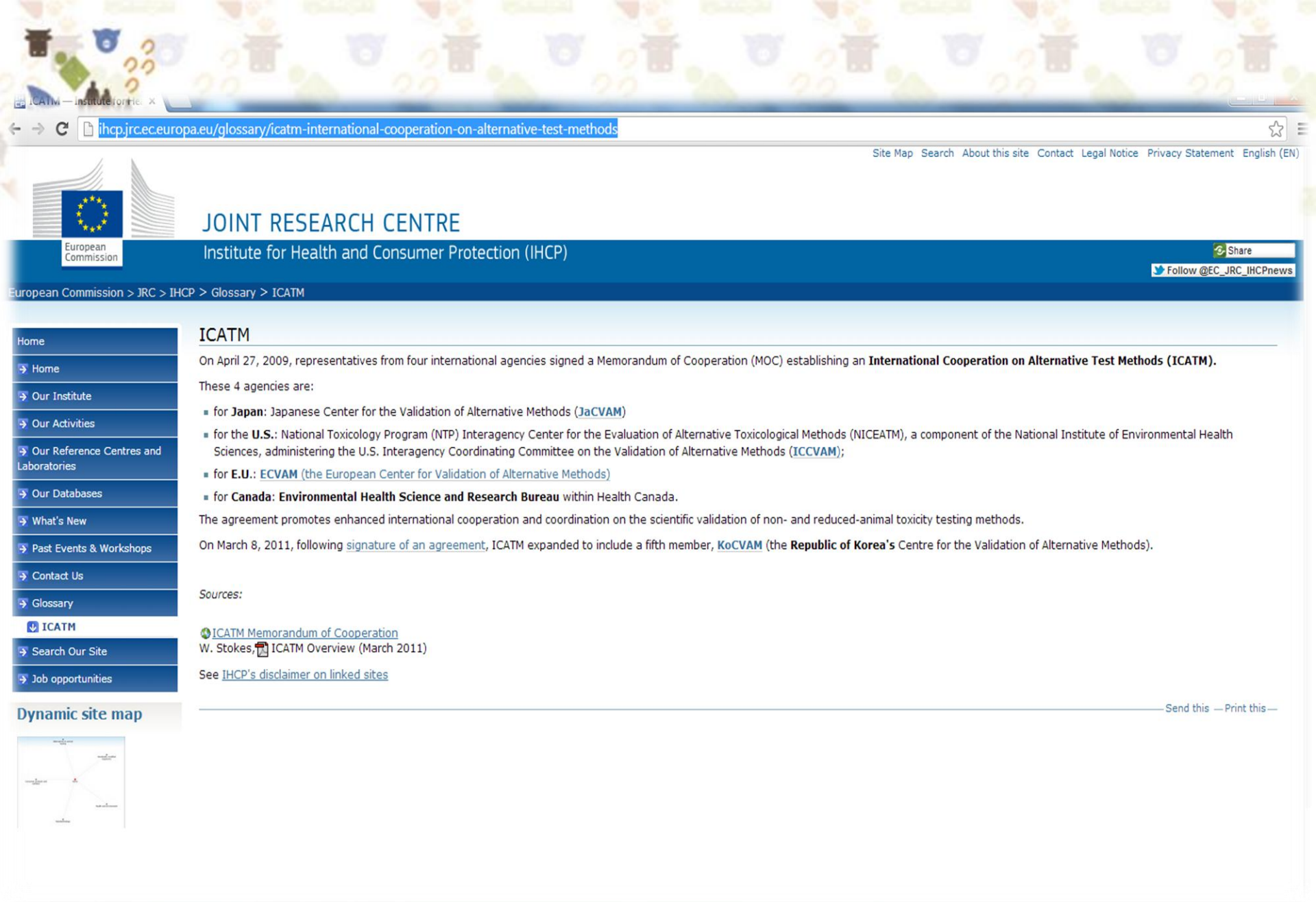
Databases

EURL ECVAM manages or co-manages the following databases:

- The **ChemAgora portal**
- The **Chemical Lists Information System (CheLIST)**
- The **DataBase service on ALternative Methods, DB-ALM**
- The **Endocrine Active Substances Database (EASIS)**
- The **EURL ECVAM Genotoxicity and Carcinogenicity Consolidated Database of Ames Positive Chemicals**
- The **JRC QSAR Model Database**
- The **EURL ECVAM Search Guide**
- The **Tracking System on Alternative Methods (TSAR)**

Related terms

- carcinogenicity
- genotoxicity
- DB-ALM
- QSARs



http://ihcp.jrc.ec.europa.eu/glossary/icatm-international-cooperation-on-alternative-test-methods

VALIDATED ALTERNATIVE METHODS

- **Total N. 99: 79% Toxicity testing; 19% Quality Control (batch testing)**
  - ***In vitro*: 58 (the majority are screenings)**
  - ***In vivo*: 24**
  - ***Ex vivo*: 10 (e.g., isolated rabbit eye test, whole rat embryo assay, rat skin trans-cutaneous electrical resistance (TER)assay, etc.)**
  - ***In vitro/In vivo*: 4**
  - ***In chemio*: 1**
  - ***N.A.*: 2 (deletion of *in vivo* batch testing after consistency, exemption for re-qualification)**

Validated *versus* valid methods

validated

- **reliability**
- **reproducibility**
- **predictivity**

PARERE*

ECVAM
ESAC

OECD

valid

- **scientific data**
- **reliability is proven**

Not formally recognised!
(mainly for testing purposes)

***(Preliminary Assessment of REgulatory REvance)**

By courtesy of Dr Sonja Beken, EMA

Alternatives in the political agendas

The 3Rs: a political agenda

- **Increasing Regulatory incentives on 3Rs**
- **Directive 2010/63/EU, replacing Directive 86/609/EEC, anchors firmly the 3Rs principle in EU legislation**
- **Regulation No 1223/2009 on Cosmetic products introduces a ban on testing and marketing**
- **Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH, entered into force 1st June 2007) and other legislation on chemicals introduce the 3Rs principle, and contain stringent provisions on:**
  - **Testing and waiving**
  - **Compulsory data-sharing in order to reduce animal testing**

The Joint CVMP/CHMP JEG 3Rs

Federal Agency for Medecines and Health Products

Joint CVMP/CHMP ad-hoc Expert Group on the application of the 3Rs in the development of medicinal products (JEG 3Rs)

- to provide advice and recommendations to the Committees on all matters relating to the use animals in regulatory testing of medicinal products
- Composition: experts from CXMP, relevant Working Parties (QWP, SWP, BWP, VWP, SWP-V, EWP-V, IWP-V) complemented by specified experts
- Meetings in 2011: 22-23 June & 27 October
- Tasks:
  - Identification of opportunities for implementation of 3Rs in regulatory testing
  - Coordinating, facilitating and prioritising EMA activities within the 3Rs arena
  - Establishing strong ties with EDQM and ECVAM (PARERE!)
  - Training on 3Rs for experts working within the field of medicinal products regulation
  - **Contribute to development of guidelines in which 3Rs issues are applicable in collaboration with relevant Working Parties**
  - Provide information and advice on 3Rs to stakeholders
  - Consider how progress on 3Rs issues can most usefully be used to influence development of regulatory guidance at an international level through ICH, VICH etc

FAMHP/SB
26/09/2011

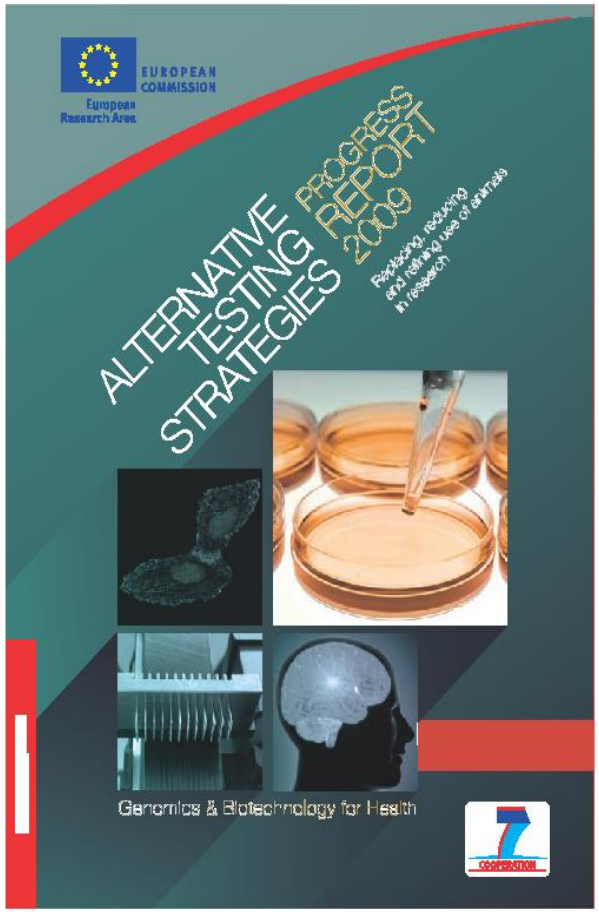
15.be

By courtesy of Dr Sonja Beken, EMA

INVESTMENTS

ALTERNATIVE METHODS – CHEMICALS

EU Research policy



EU **Framework Programmes** for Research and Development, more than **200 million €** for research on alternative methods, of which more than 100 million over the last 5 years.
AXLR8(*) provides annual reports on development and outcome of EU Research on Alternative Approaches

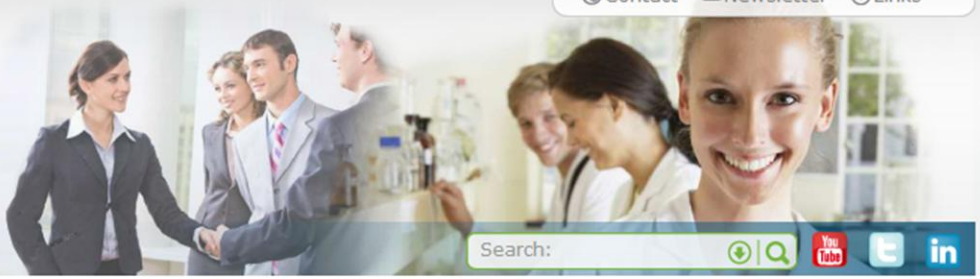
http://axlr8.eu/

(*) Accelerating the transition to a toxicity pathway-based paradigm for chemical safety assessment through internationally co-ordinated research and technology development

www.imi.europa.eu

Contact Newsletter Links

Innovative Medicines Initiative



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- News, Events & Media
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PARTNER SEARCH | EDUCATION & TRAINING | SMALL & MEDIUM-SIZED ENTERPRISES | INTELLECTUAL PROPERTY

Members area

- Governing Board
- States Representatives Group
- Scientific Committee

THE INNOVATIVE MEDICINES INITIATIVE

The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines for patients.

IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.

IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA.

efpia

INDICATIVE TOPIC TEXTS FOR IMI 2-CALL 1

Indicative topic texts for **IMI 2-Call 1** topics are now available. More information about the new Call will be available once the topics have been finalised.

for more info

ONGOING PROJECTS

Get on-course!

With over 5 000 courses, on-course, run by the EMTRAIN project, is Europe's most comprehensive biomedical R&D postgrad course portal

... more

All projects

IMI 2 FUTURE TOPICS

The IMI 2 **Strategic Research Agenda** and the first **topics** under consideration for the **IMI 2 Calls for proposals** are now available.

IMI 2 will pave the way for **breakthrough vaccines, medicines** and **treatments** to tackle major health challenges.

more

IMI NEWSFLASH

05/06/2014 : @MichelGoldman explaining at #bv14innov how IMI helps move therapeutic innovation forward http://t.co/4X9MCEW9AV

05/06/2014 : IMI education & training programme SafeSciMET launches 3rd course cycle on safety sciences 4 medicines http://t.co/UsC4tlQYch Register now!

05/06/2014 : You can watch IMI's @MichelGoldman taking part in Biovision #bv14innov via http://t.co/VtHOfMHlIm @BiovisionForum

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NEWSLETTER

Read & subscribe more

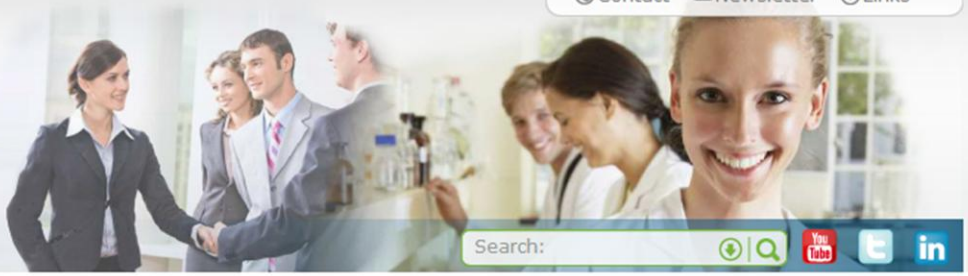
AGENDA

- 21/05/2014 - IMI Stakeholder Forum 2014...
- 20/05/2014 - IMI - JDRF Diabetes Patient F...
- 25 - 27/03/2014 - DIA EuroMeeting...

www.imi.europa.eu/content/etox

Contact Newsletter Links

Innovative Medicines Initiative



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UPCOMING EVENTS

- There are no upcoming events.

Back to overview

eTOX

Integrating bioinformatics and chemoinformatics approaches for the development of Expert systems allowing the *in silico* prediction of toxicities

Summary

The eTOX project partners will develop innovative strategies and novel software tools to better predict the safety and the side-effects of new candidate medicines for patients. Reliable prediction of side-effects in the initial phases of drug development lowers the failure rate in later phases, significantly reduces the number of animal tests needed and accelerates the development of new drugs.

The eTOX scientists will use the complex relationships between the structure of a substance, its metabolism and disposition, and its toxic effects in the body. The combination of this knowledge will enable them to create more reliable computer models to better predict potential side-effects that would otherwise only be discovered in a later stage of the drug development or when the drug is already on the market.

more

Achievements & News

eTOX in the spotlight in special issue of Molecular Informatics

IMI's drug toxicity project eTOX features in a special issue of the

Facts & Figures

Start date	01/01/2010
Duration	60 months

Contributions	**€**
IMI funding	4 737 991
EFPIA in kind	7 909 119
Other	1 238 361
Total costs	13 885 461

Links and Documents

Project website: www.e-tox.net

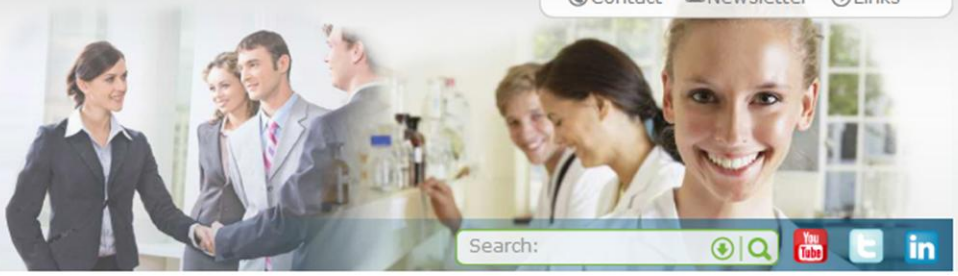
IMI funding per project participant

Publications

www.imi.europa.eu/content/mip-dili

Contact Newsletter Links

Innovative Medicines Initiative



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UPCOMING EVENTS

- There are no upcoming events.

Back to overview

MIP-DILI

Mechanism-Based Integrated Systems for the Prediction of Drug-Induced Liver Injury

MIP-DILI

Summary

Many medicines are harmful to the liver, and drug-induced liver injury (DILI) now ranks as the leading cause of liver failure and transplantation in western countries. However, predicting which drugs will prove toxic to the liver is extremely difficult, and often problems are not detected until a drug is already on the market. For the first time, the IMI project MIP-DILI brings together Europe's top industrial and academic experts in the field. Together, they will develop new tests that will help researchers detect potential liver toxicity issues much earlier in development, saving many patients from the trauma of liver failure.

more

Facts & Figures

Start date	01/02/2012
Duration	60 months

Contributions	**€**
IMI funding	15 300 000
EFPIA in kind	11 000 000
EFPIA US	1 600 000
Other	4 500 000
Total cost	32 400 000

Participants

EFPIA

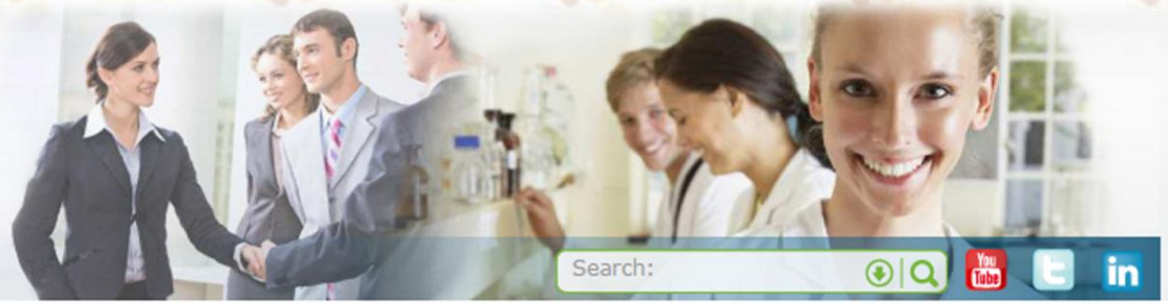
- AstraZeneca AB, Södertälje, Sweden
- Abbott GmbH & CoKG, Wiesbaden-Delkenheim, Germany
- Bristol Myers Squibb EMEA sarl, New York, US
- GlaxoSmithKline Research and Development Ltd, Middlesex, UK
- H. Lundbeck A/S, Valby, Denmark

Links and Documents

Project website: www.mip-dili.eu

IMI funding per participant

Publications



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LATEST NEWS

07/10/2014 : @eupatients Congratulations Team EUPATI, and good luck to all the students!

07/10/2014 : RT @eupatients: First EUPATI course launched today: 53 trainees starting with webinar and first edu module http://t.co/t7qYhxHjof @EUPATIen...

UPCOMING EVENTS

- **18 - 18/11/2014 -** Financial Management

Back to overview

STEMBANCC

Stem cells for biological assays of novel drugs and predictive toxicology

Summary

The aim of the STEMBANCC project is to generate and characterise 1 500 high quality human induced pluripotent stem (iPS) cell lines that can be used by researchers to study a range of diseases, including diabetes and dementia, and test for drug efficacy and safety. The cell lines will help to improve and speed up the drug development process, and ensure that patients benefit from more effective and safer drugs.

more

Achievements & News

STEMBANCC recruitment on track

IMI's stem cell project StemBANCC is advancing well with the recruitment of patients and control individuals (subjects). So far, around 50 subjects have been recruited to disease cohorts such as Alzheimer's disease, neuropathy, ...more

Facts & Figures

Start date	01/10/2012
Duration	60 months

Contributions	**€**
IMI funding	26 000 000
EFPIA in kind	21 000 000
Other	8 600 000
Total cost	55 600 000

Links and Documents

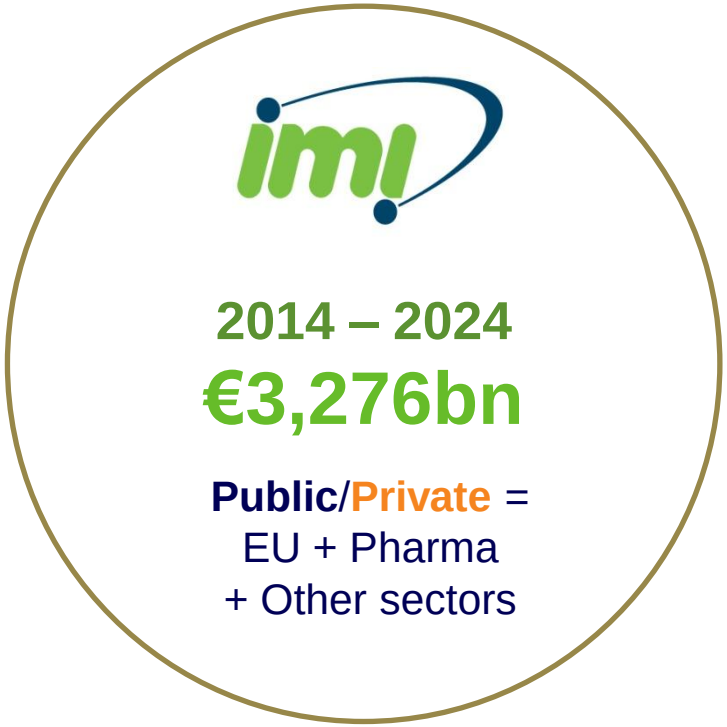
Project website:
www.stembancc.org

IMI funding per project

Innovative Medicines Initiative:
EU Partnership for Health

FP7

H2020



ec.europa.eu/enterprise/epaa/index_en.htm

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Enterprise and Industry

EPAA

- About EPAA
- Partners
- Platform on Regulation
- Platform on Science
- 3Rs Awards Prize
- News and events

European Partnership for Alternatives Approaches to Animal Testing

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is an unprecedented voluntary collaboration between the European Commission, European trade associations, and companies from seven industry sectors.

The partners are committed to pooling knowledge and resources to accelerate the development, validation and acceptance of alternative approaches to further the replacement, reduction and refinement (3Rs) of animal use in regulatory testing.

epaa
The European Partnership
for Alternative Approaches to Animal Testing

News and Highlights

SEURAT-1 2014 annual meeting (5-6 Feb 2014, Barcelona) showcases new results and challenges in alternative methods to animal testing - Meeting flash report - Read more

EPAA 9th Annual Conference: More Predictive Safety Science for a more competitive Europe – 13 November 2013 – Brussels

EPAA Vaccines Consistency Approach – Clostridial Vaccines Workshop #2 - Flash report

SEURAT-1/EPAA 1st Stakeholder event - Flash report

3rd SEURAT-1 annual report

The European Partnership for Alternative Approaches to Animal Testing

APPLICATION OF ALTERNATIVE METHODS THROUGH THE CONSISTENCY APPROACH FOR IMPROVED VACCINE QUALITY CONTROL

STRONG INTEREST OF INDUSTRY AND REGULATORS IN NEW EPAA PROJECT

At the occasion of a Workshop organised by the EPAA on April 7, 2011, representatives from industry and regulators (including EMA, EDQM, UK, Netherlands, France, Belgium, Germany, US and Canada) agreed to participate in a project on the application of alternative methods through the consistency approach for improved vaccine quality control. The consistency approach is already used for the release of vaccines of the most recent generation of vaccines. The purpose of the project is to successfully implement the approach for the routine release of conventional vaccines.

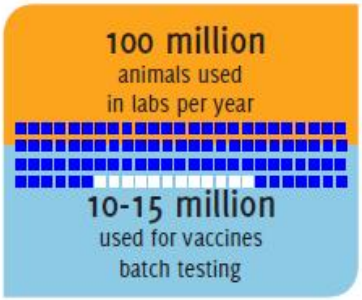
Participants took note of the strong support of the EU Commission for the EPAA and its role in the EU policy context. For **John Dalli**,speaking at the 2011 EPAA conference, EPAA is a «model of how to work effectively across different sectors, and in co-operation between regulators, industry and other stakeholders". In recent interviews, **Antonio Tajani** stressed the need «to explore the full potential of the virtuous circle of innovation resulting in better animal welfare, and animal welfare resulting in better science"). **Janez Potocnik** suggested «to try to improve the outreach of EPAA to the regulatory risk assessors and risk managers»

1 MAJOR SCIENTIFIC, ANIMAL HEALTH AND ECONOMIC FEATURES OF THE CONSISTENCY APPROACH

Control of batch release of vaccines for human and animal is one of the biggest use of animals for testing in the pharmaceutical sector. Estimates suggest that worldwide more than 100 million animals are used in laboratories, of which between 10 – 15 % for vaccines batch release testing. The majority of these animals are utilized for compliance to regulatory requirements.

There have been great achievements in the validation and implementation of alternative methods to animal testing used for routine quality control over the last years and today in vitro testing is developed for new candidate vaccines and implemented in their routine release quality control at licensure.

Whilst there have been evolution of the release process approach both on the side of Control Authorities and manufacturers, there is still room for improvement: at the level of regulatory authorities for facilitating the introduction of new release concept on the basis of the consistency approach, at the level of test "users" to engage on alternatives development.



Implementation of the consistency approach in batch release testing is expected to result in scientific, economic and animal welfare benefits without jeopardizing the quality, safety and efficacy of the vaccines:

- More powerful and reliable analytical tools for lot release
- Less cumbersome and time consuming Quality control (a few days instead of 2 months)
- Faster access of vaccine lots to the patients/animals

Investments in 3Rs in EU

EUROPEAN COMMISSION
Research & Innovation

COLIPA
The European Cosmetics Association

SEURAT-1

Paracelsus (1493-1541):
"The dose makes the poison"

Towards the Replacement of *in vivo* Repeated Dose Systemic Toxicity Testing

SEURAT, Safety Evaluation Ultimately Replacing Animal Testing

A joint €50m EC – Colipa project on replacement in repeated dose systemic toxicity testing

Grouping seven distinct projects

With an impact on many different areas including drug development, industrial chemicals, biocides etc….

http://www.seurat-1.eu/

EU-ToxRisk Project (€30m)

- EC-funded project as a follow-up H2020 project of the FP7 SEURAT-1 project

- Duration: 6-year flagship project for the EC (start 01/01/2016)

- Scope: to explore repeated dose toxicity and reproductive and developmental toxicity studies (further expanding on case studies and knowledge developed within SEURAT-1)

- Collaboration of 40 institutions including **European regulatory bodies**, **universities**, **companies**, **SMEs and industry federations (Cosmetics Europe)**

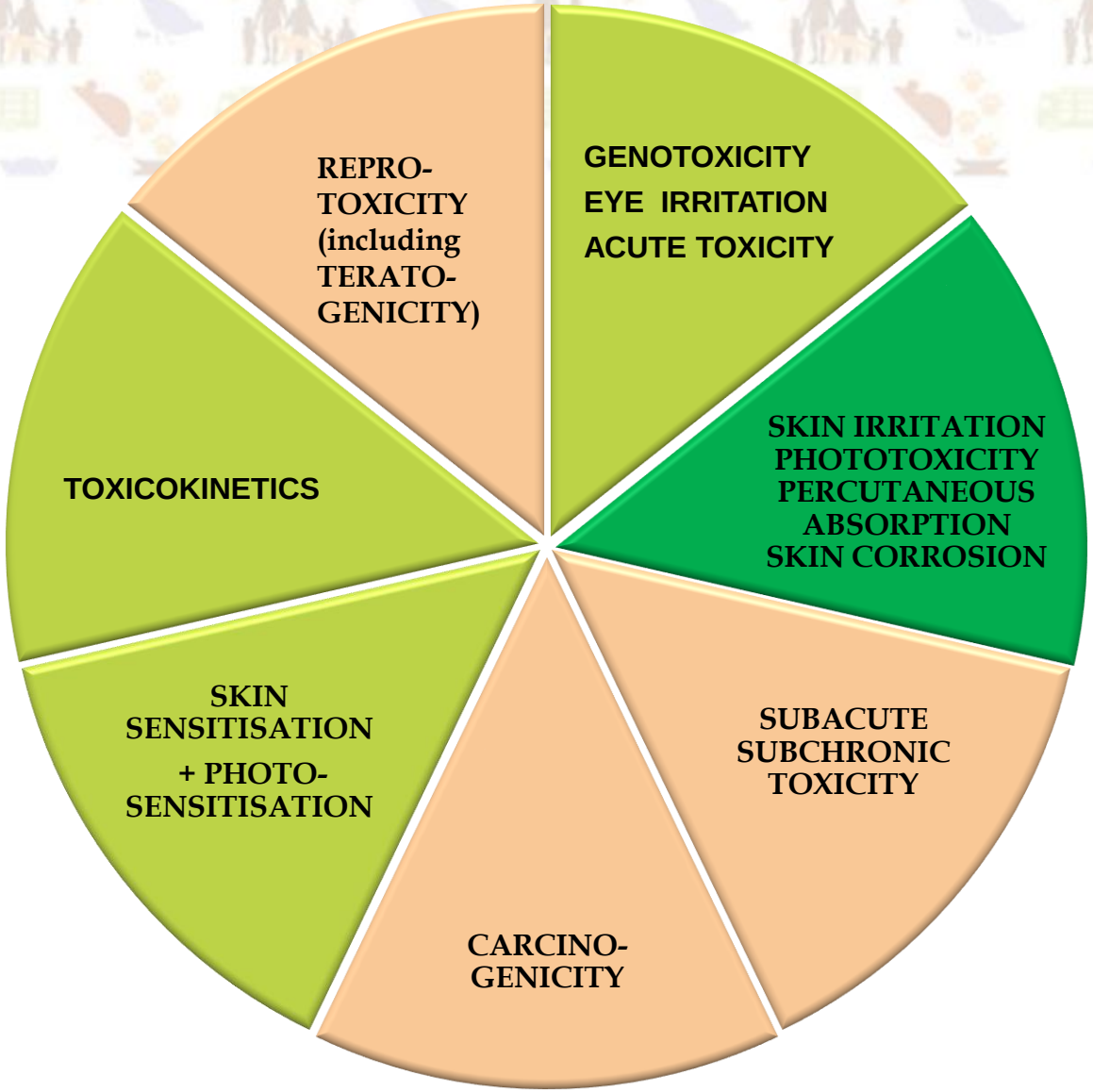
- A scientific advisory board will follow closely the activities of the project.
- A call was made on implementing rapidly a website on the EU-ToxRisk project (**by the end of 2016**)

- Project General Assembly will be held in June 2016 to discuss the most relevant case studies and decide which will be pursued/ investigated further.
- **First results from the project are estimated to be provided in 2018**

The Cosmetic Regulation
A long story

- **1993**: Directive 76/768 amended to ban marketing of animal tested cosmetics from 1998 (Council Directive 93/35/EEC; the 'sixth amendment')
- **1997**: Commission Directive 97/18/EC postpones the marketing ban to 2000
- **2000**: Commission Directive 2000/42/EC postpones the marketing ban to 2002
- **2003**: Directive 2003/15/EC (marketing of cosmetics containing ingredients tested on animals); intended to put an end to animal testing by imposing bans on:
  - Testing finished cosmetic products and ingredients on animals (testing ban: 2009)
  - Marketing finished cosmetic products which have been tested on animals or which contain ingredients which have been tested on animals (marketing ban 2009/2013) (marketing of cosmetics containing ingredients tested on animals for all <u>but three endpoints banned</u> (2009) <u>irrespective of availability of alternatives</u>)
- Final phase of marketing ban 2013 (additional three endpoints) subject to eventual revision if alternatives are not available
- The Directive 2003/15/EC has been re-cast and it has been moved from a Directive to Regulation (EC) No 1223/2009 (timeline: 11th July 2013 for coming into force in Member States)

Status of AAT Science: prospects by 2020



RESEARCH

ADVANCED

COMPLETED

Kindly provided by Cosmetics Europe

Esiste UNA TOSSICOLOGIA ma diverse modalita` d'uso dei dati tossicologici nei diversi settori

HAZARD ***VS*** **RISK**

ELEMENTI INDISPENSABILI PER LA VALUTAZIONE DI RISCHIO (RISK ASSESSMENT)

- **Comprensione dei meccanismi che portano all'evento tossico (Adverse Outcome Pathway) → Rilevanza del modello per il paziente/consumatore**

- **Livello di esposizione alla sostanza (ADME - *Dosis facit venenum*)**

- **Rapporto rischio-beneficio (medicine)**

COMMISSIONE
EUROPEA

Bruxelles, 5.12.2013
COM(2013) 859 final

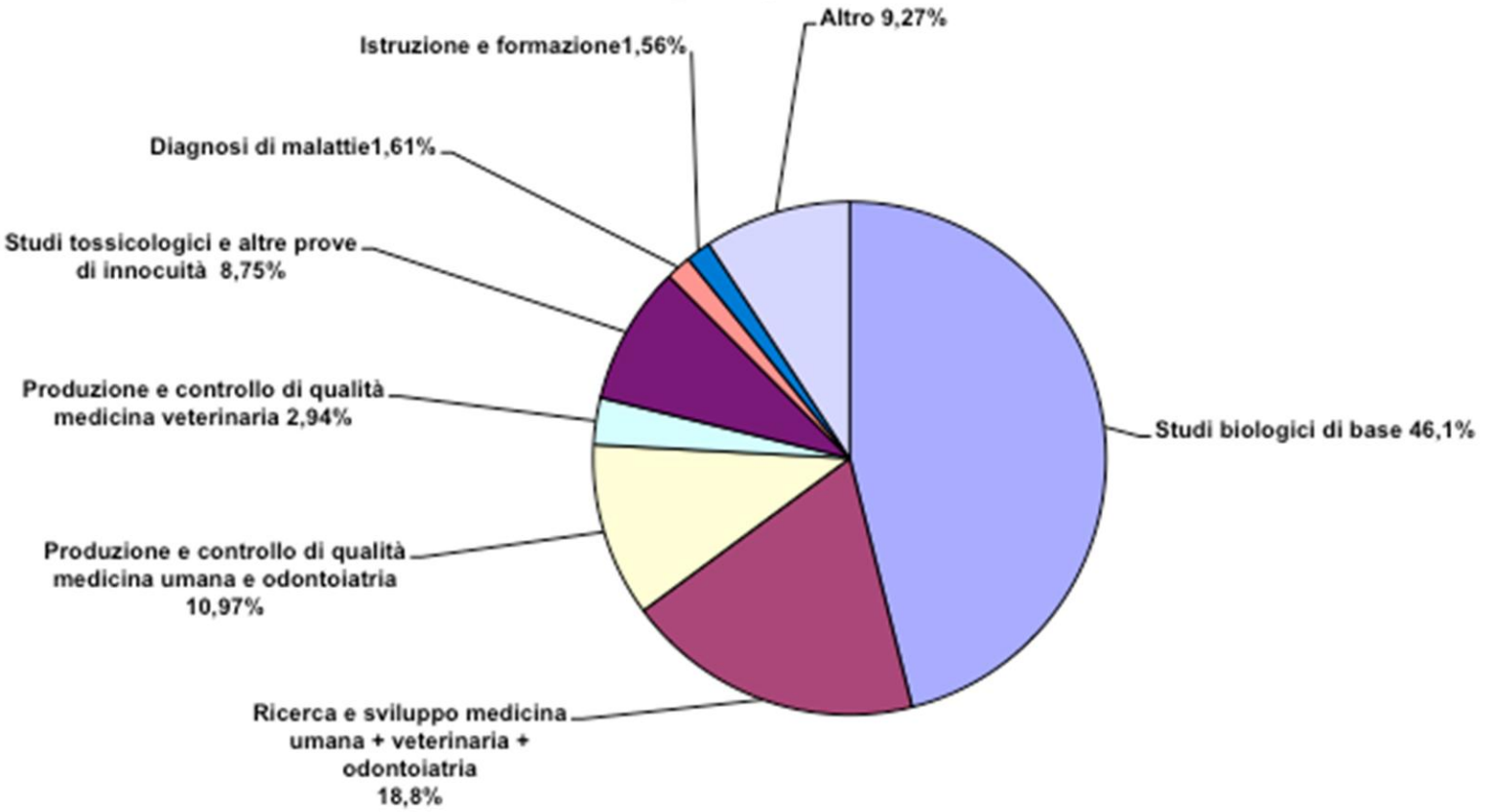
RELAZIONE DELLA COMMISSIONE AL CONSIGLIO E AL PARLAMENTO EUROPEO

Settima relazione sulle statistiche riguardanti il numero di animali utilizzati a fini sperimentali o ad altri fini scientifici negli Stati membri dell'Unione europea

{SWD(2013) 497 final}

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM%3A2013%3A0859%3AFIN%3AIT%3APDF

Figura 2
Finalità degli esperimenti



CONCLUSIONI

- **“Alternativo”≠ “sostitutivo”**
- **Metodi “alternativi” ufficialmente validati limitati a tossicologia regolatoria e QC (Farmacopea)**
- **~€500m investiti (EC + industria)**
- **Modelli “sistemici” non ancora disponibili**
- **Leggi in materia scientifica devono tener conto dello stato di avanzamento scientifico/tecnologico**
- **Esiste UNA TOSSICOLOGIA applicabile ai diversi settori**
- **Differenza tra pericolo e rischio (Hazard *vs* Risk)**
- **Sempre maggior allineamento tra diversi settori**