Potential Improvement in the Development of Alternative Methods: Needs in Risk Assessment of New Technologies vs Use of Alternatives

November 24/25, 2007
Brussels, B
Sheraton Airport

Alternative Methods: Need vs Experience of Two Decades

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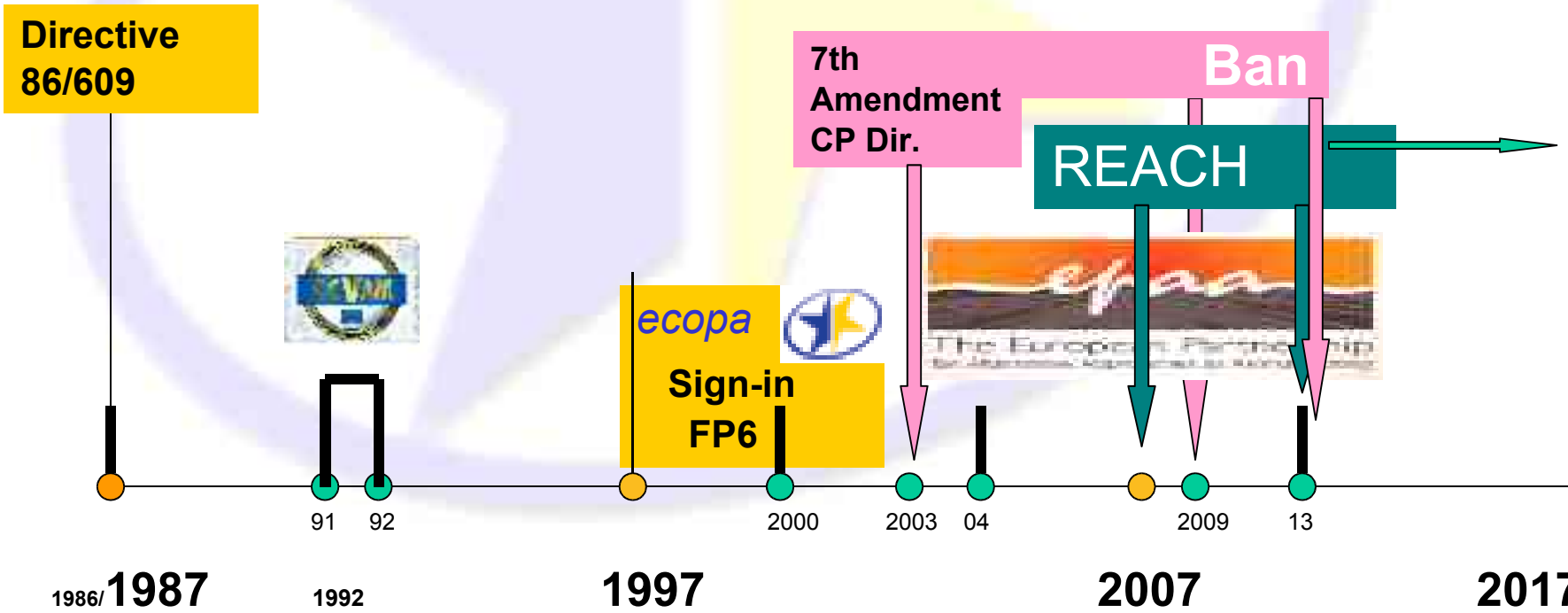
Bayer AG, Leverkusen, D

November 24/25, 2007, Brussels, B

Time to check and think – two decades

Another one or two decades?
And where do we go/stand?



Expectations

- in the past:

„Hopes“

- For a **substitution** of Draize eye test, or
- Acute toxicity
- Repeated dose toxicity
- Reprotoxicity

“Substitution”

- means what?

- **Replacement**
- **Reduction**

or “only”

- **Refinement ?**

(such as the two- reduced to one-generation study)

From validated, world-widely-accepted,
to „suitable for REACH“?
Because the real one is not yet available?

Was it over-selling?

Was it ignorance?

Was it neglecting solid science?

And not listening to warnings of some solid scientists?

Comm. Verheugen at the Nov. 5-epaa-meeting*:
Quote: „…We will not accept postponing ban of testing of cosmetics and marketing acc. to the 7th Amendment…
We can not lessen our efforts, neither on
the side of the Commission nor on the side of the industry.“

*http://ec.europa.eu/enterprise/epaa/conf.htm

So, where do we stand after two decades?

-of ECVAM, *ecopa*, epaa etc.

-and an investment of roughly more than 250 Mio €

- **Did we adhere too rigidly to a chimaera?**
  i.e. a perfect alternative system

Which was

-a „nice target“ **(but just to remind you of a former EU target 50% animal testing by 2000!)**

-politically wanted

Isn‘t it time to change,
and become – finally – realistic?

What do we have?

FORMALLY VALIDATED ALTERNATIVE METHODS IN THE EU:

- **acute oral toxicity**
- **skin corrosivity : TER, EPISKIN®, EPIDERM®, CORROSITEX®**
- **skin irritation : EPISKIN®**
- **skin sensitisation : LLNA**
- **phototoxicity : 3T3 NRU-PT**
- **dermal absorption with human/pig skin**
- **mutagenicity**
- **embryotoxicity : WEC, MM, EST**

What we might have:

→ ***In vitro*** **eye irritation (ECVAM, 2008?)**

LOCAL TOXICITY

→ ***In vitro*** **prediction non-toxicity: cytotoxicity testing (ECVAM, 2008?)**

→ ***In vitro*** **muta/carcinogenicity: cell transformation assays (ECVAM, 2008?)**

→ ***In vitro*** **skin models for genotoxicity (ECVAM, ?)**

→ ***In vivo*** **extended 1-generation study (ECVAM, 2008?)**

→ ***In vitro*** **endocrine disrupter tests (ECVAM, 2008?)**

SYSTEMIC TOXICITY

And what do we need?

- ACUTE TOXICITY (dermal, inhalation)
- PHOTO ALLERGY
- SUBACUTE TOXICITY
- CHRONIC TOXICITY
- REPRODUCTIVE TOXICITY
- TARGET ORGAN & SYSTEMIC TOXICITY
- CARCINOGENICITY (non-genotoxic compounds)
- BIOKINETICS

and how about the „new“ technologies?

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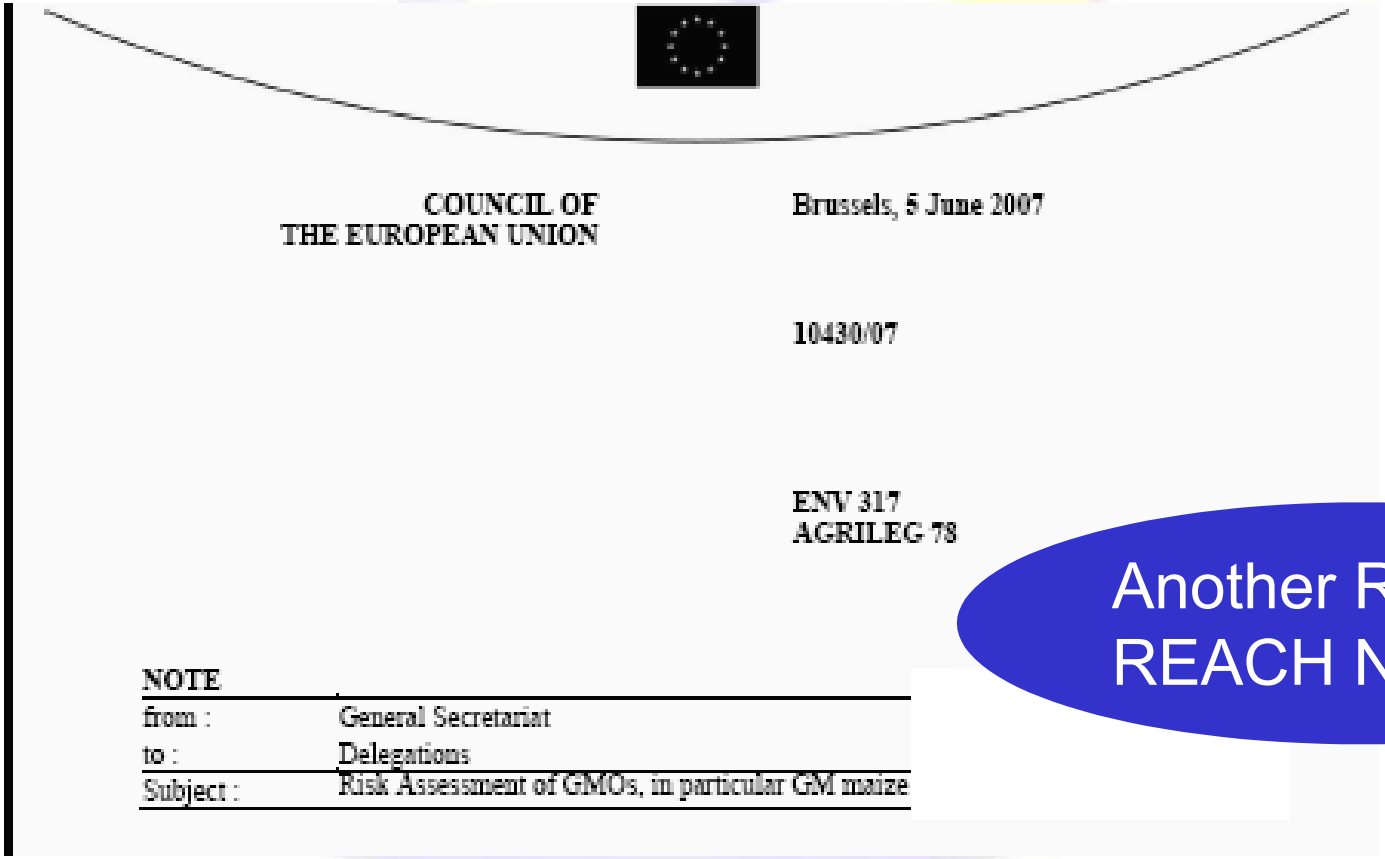


COUNCIL OF
THE EUROPEAN UNION

Brussels, 5 June 2007

10430/07

ENV 317
AGRILEG 78

NOTE

from :	General Secretariat
to :	Delegations
Subject :	Risk Assessment of GMOs, in particular GM maize

Another REACH?
REACH No. 2?

…“In conclusion, Austria suggests that a new long-term feeding study using *GMO* maize, based on the latest toxicological state of the art and on appropriate methods to assess the biological performance of the GMO-fed animals, should be undertaken. Such a study would of course need a much longer observation period as a subchronic toxicity study.“

But we have come a long way already…

from

- Screening tests in pharmaceutical industry
- 3Rs discussions not only on
  country national level,
  European level,
  now on a global level

ICH JCVAM ICCVAM

- Alternatives put forward by ECVAM and brought up as a topic permanently
- Major funding

Activities of *ecopa*

in the past:

- Annual Workshops
- Sign-in-action against EU Chemical Policy, driving for a REACH + alternatives in FP 6/7
- Impact Report, Animal Calculator, CONAM project
- eSi for new research
- Call for involvement of regulators at epaa

and in the next decade?

- Work with the industries and academia to convince regulators of realistic approaches

Critical Questions

to all of us:

- **If we would not have spent already > 236.5 plus Mio €*, where would we invest today?**

- **And if we call part of it „sunk money“, isn‘t it the time to go for the usual next step? Assuming that after an upfront-investment the next phase is self-supportive and carrying itself?**

- **And what are we going to do with the new and „different“ technologies?****

* see S Webb-presentation for EU-countries

** see HJ Ahr-presentation for technology challenges

Logical Next Step:

- Rather than calling for and requesting more funds from the EU (or investing industries),
- Let‘s start/START realistic strategy-discussions!
- Let‘s start / START-UP identifying barriers in an active way!

Let‘s start / START-UP a political discourse also, reg. Union Politics

We are still

not ... !

Cell/Gene „issues“

-omics

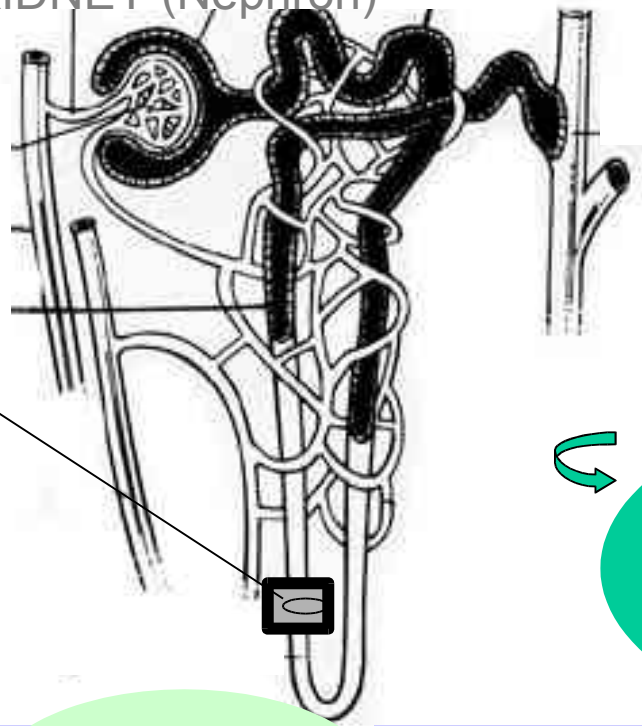
Substance „issues“

Media „issues“

- “In between“ toxic
- Cytotoxic by itself
- Active in pathways present/not changed/not

- Cells go on, but not in vivo,
- Cancer from human
- „Smoker cells“, donor issue

Example:
KIDNEY (Nephron)



- Continuous change
- Changes (genes) happening over time: permanently and unpredictably!

Use for mechanistic studies, not toxicity!

- Metabolic capability
- Impaired lipids,
- Transport, ongoing function,
- Hormones

- Nutrients
- Endproducts
- Bi-directional transport
- Flow

Questions

- So, after all these years,
  and funds,
  what are we left with?

„Kind of an intermediate plastic stage“
(Advisory Board Member of a FP-project)
on toxicogenomic studies

- Always the same questions
  - What criteria? „Is the model ok“?
  - Performance criteria, variability
  - Sensitivity, small reference cpds list
  - Time points etc.

- Target: predictivity vis à vis mechanistic approach

Balance:

- So, in summary, we are not there yet

- But, we have made progress, credit to all involved, and credit to ECVAM for preparing and making the global step

- By now, everybody knows about the importance of alternative-development

Conclusions

- **We do not need**
  a high quantity of methods that will not make it, not "useable methods" in the REACH-legislation-sense

152 plus

- **Therefore, we do need the proper road map (like in the START-UP -project): focus**

- **We do need thoroughly engineered useable methods that are or will be accepted, because they fill a need**

5

(Actually, tests like the LLA might need further improvement, but will prevail on the long term)

BUT: we will also still need funding - maybe more for the basic reseach (for the new technology products!)

Conclusions

WE DO NEED ADDITIONAL FUNDING!

-for basic reseach
-for the new technology products

THAT SHOULD BE PART OF THE 7TH FP, BUT OF THE FUNDS OF THE NEW ERC*

*European Research Council

Thank you for your attention!

Let me wish you

- a Merry Xmas and
- a Happy New Year!

A chimaera*

Let‘s become real!

***Webster‘s Dictionary:**
„horrible creature of the imagination; wild or impossible idea or fancy“

Pictures of the Past…

…ecopa Annual 10/2000…

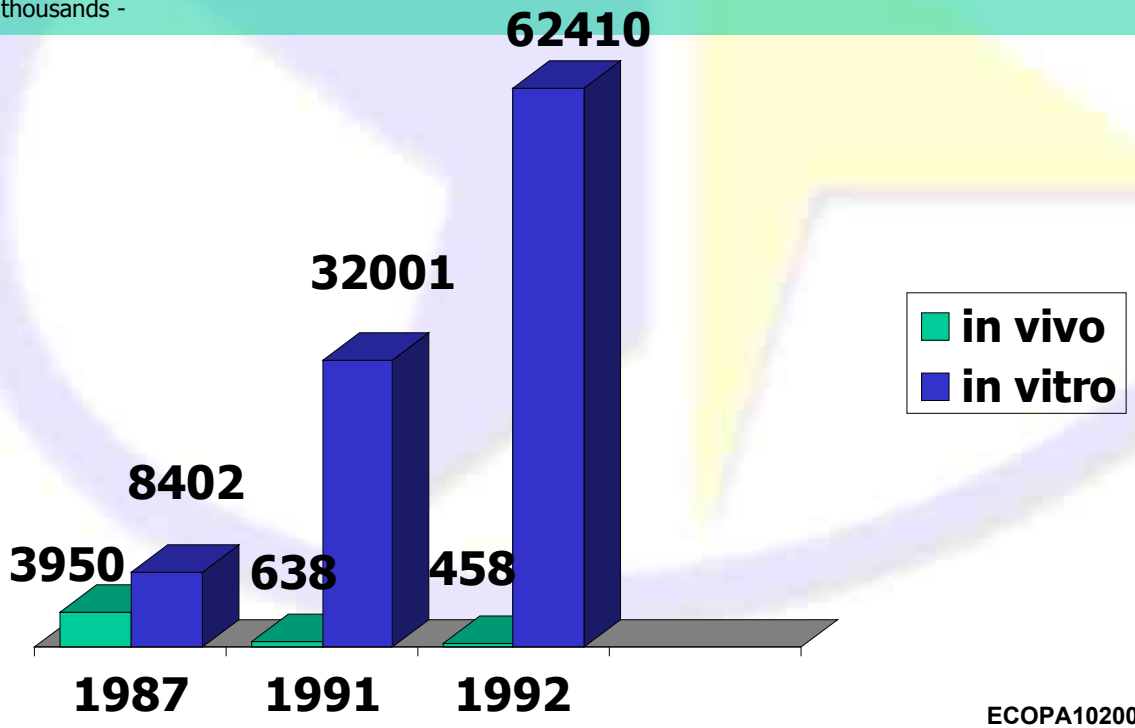
ecopa
european consensus-platform for alternatives

…seems like *yesterday*…

Impact of New Alternative Technology on Reduction of in vivo-Experiments

Increase in number of in vitro-tests for substance screening for efficacy in a pharmaceutical cardiovascular reasearch institute of industry (impact of new methodology and introduction of robot screens)

- number in thousands -



Alternatives in Testing of Vaccines: Request of Industry

Press Communication Behringwerke AG

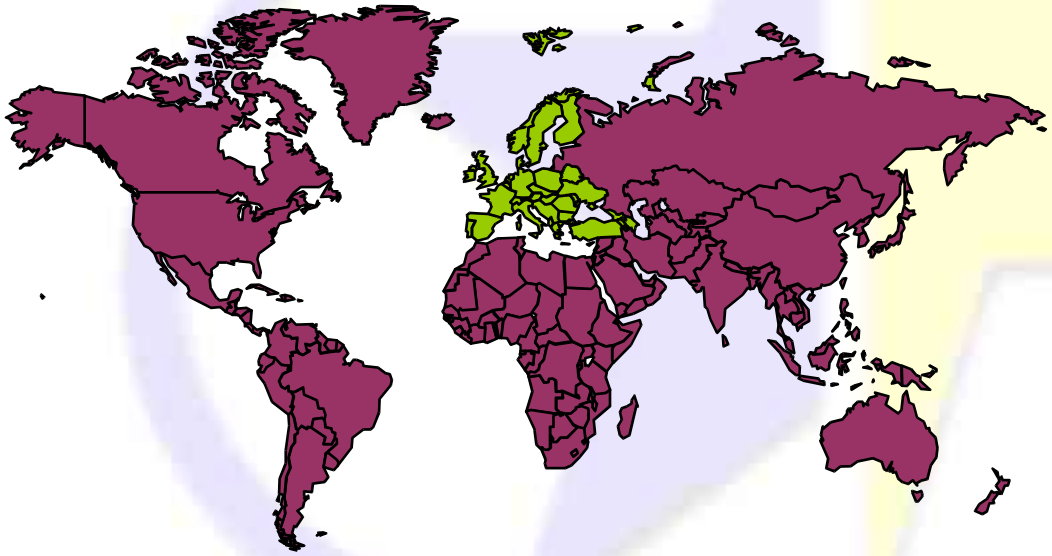
April 1992

Behring Scientists call upon politicians and authorities

Behringwerke have addressed the responsible scientific insitutions of authorities with proposals to reduce animal experiments. Pharmacologists of Behringwerke have listed in total **eleven** different tests on lab animals requested for development and quality control of vaccines and plasma products, which could be either cancelled without any substitution or could be altered in such a way that the number of animals required would be drastically reduced. (...)

With these suggestions proposed to politicians and authorities, Behringwerke expects to contribute to the abolishment of animal experiments, that are not justifiable from a pharmaceutical science point of view.

Aspects of Further Implementation and Development of Alternative Methods: they are global!



To exert influence and have an impact:

you have to argue EUROPEAN at least!

Funding of alternative method development over two decades (cumulative)