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New Technologies: Threat or Chance for Alternative Method Development

- **Introduction: Early Signals, Hightech vs. Nature**
- **Regulatory Background: Assessing Risks**
- **Precautionary Principle: the „easy EP-Approach“**
- **„The Pipeline is drying up“ for Alternatives**
- **Hypothesis: Threat or Chance?**
- **Conclusions**

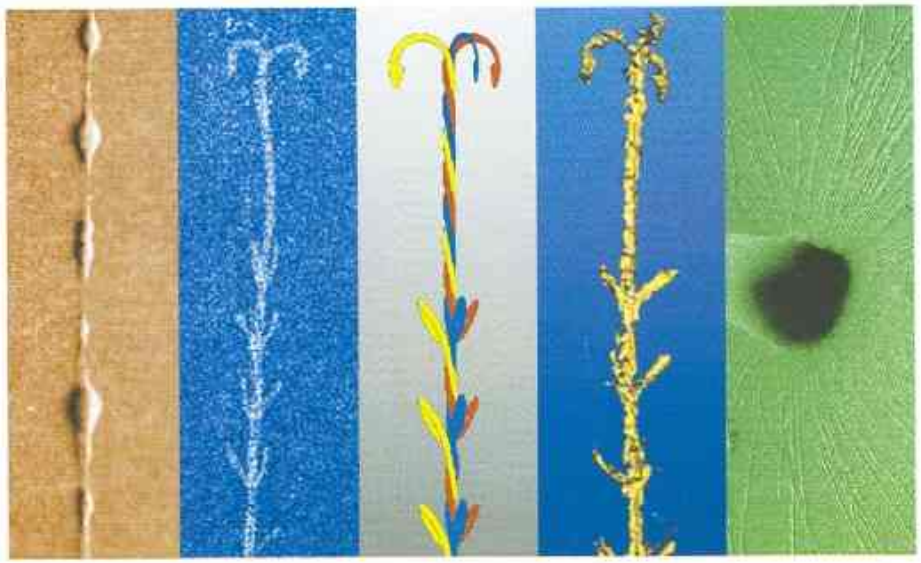
Introduction:

Early Signals

- New technologies or trends develop without being fully understood or recognized by the scientific, regulatory communities and the public
- Same goes for the alternative methods scene,
  Example 1: -omics → 1st ECVAM status report, not picking it up
  Example 2: Endocrine Disruptors → Environmentalists calling for massive testing
- New technologies might be regarded as a threat, but they also offer opportunities for alternative methods development as well as to improve EU competitiveness

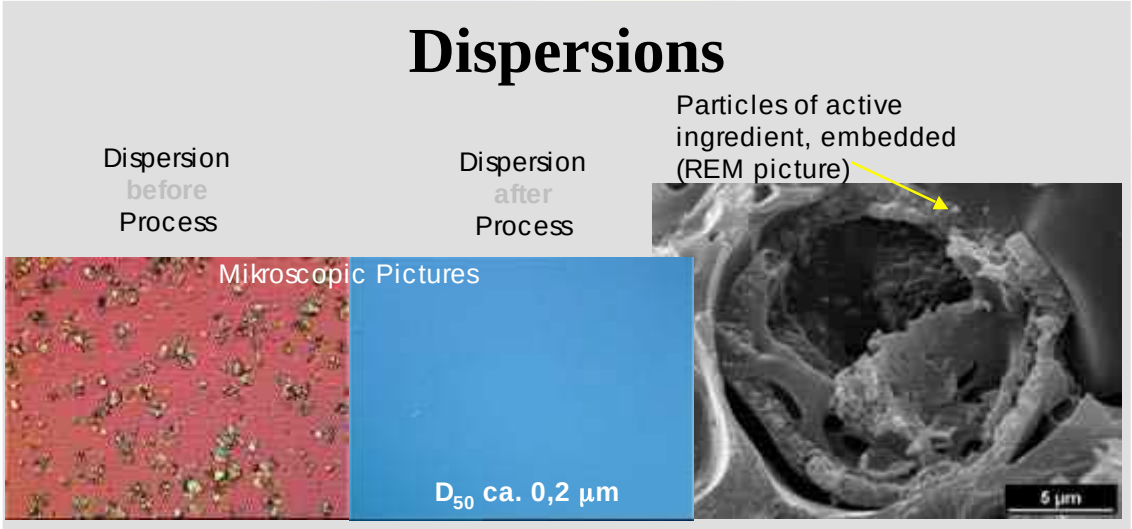

Erdal
UNIVERSAL
IMPRÄGNIER
SPRAY
NANOtec
FÜR LANGZEIT-SCHUTZ GEGEN NÄSSE,
SCHMUTZ, SALZ- UND SCHNEERÄNDER
FÜR ALLE FARBEN

Nature:



Nano pictures of the hami of Archeon thiotrix

Industry:



Newly developed formulations for substances not soluble in water

Regulatory Background: Assessing Risk

- Directives, are only reactive — regulating Pharmaceuticals, Cosmetics, PPPs (plant protection products), Biotech Ps, GMOs:

  Where are alternatives mentioned?

- „REACH out“ : testing required,
  lip service in terms of alternative method development

  ecopa‘s sign-in action
  Intervention at Commission level: Changed attitude!

Regulatory Background: Assessing Risk

- „New“ technologies: assist in finding new alternatives
  „old“ example → radioimmunoassays
  -omics → EU 6th FP projects

- Endocrine Disruption: „outdated“ testing technology –
  „improvement“ of 40 yr old assays!

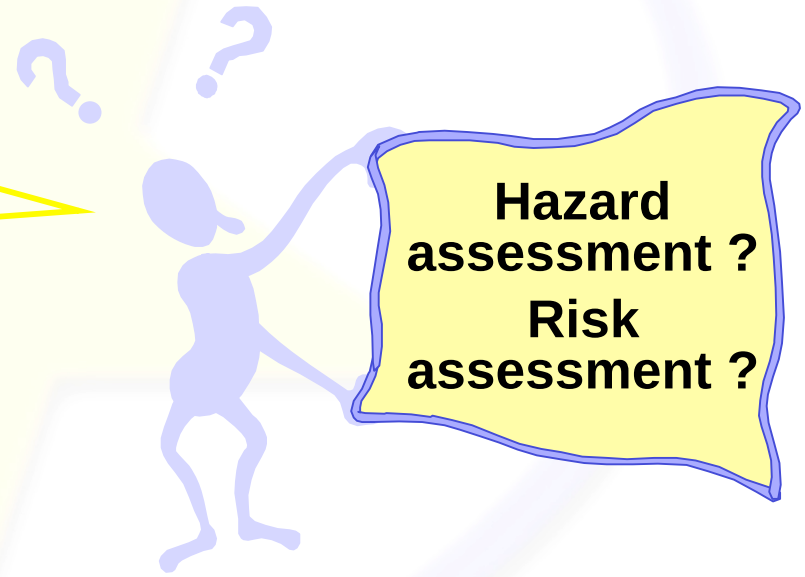
OECD: „At present, we do not have work underway for test guidelines in these areas.“…“ However, the topics of Nanotech and Biotech are very interesting to the OECD and we have work programmes in those areas.“

From a mail Drew Wagner,
Principal Administrator OECD ENV/EHS of Nov. 14, 2005

Confusion: Hazard vs. Risk

HAZARD ≠ RISK

JUST A QUESTION OF TERMINOLOGY



What is Hazard Assessment?

Determination of :

- **NOAEL values**
- **LD_{50} values**
- **nature of the toxic effects**
- **target organs**
- **mechanisms of action**

Based upon :

- **Acute toxicity**
- **Skin irritation**
- **Eye irritation**
- **Skin sensitisation**
- **28d repeated dose toxicity**
- **90d repeated dose toxicity**
- **Chronic toxicity**
- **Reproductive toxicity**
- **Toxicokinetics**
- **Mutagenicity**
- **Carcinogenicity**
- **Specific tests**

What is Risk Assessment?

- Objective quantification of probabilities and consequences of adverse effects
- It is a purely scientific enterprise

Looking for a "safe dose"

* does not exist
* estimation according to a set of rules

What is Risk Perception?

Perception of how much risk of what sort is acceptable to the consumer

Risk perception is subjective and qualitative
⇨ Public and media do not discriminate between degrees of hazard or risk

Precautionary Principle:

The “easy” way out for the EU, EP, Commission?

PRO‘s

- inhibits new technologies being introduced into EU
  (also those for alternative method development)
- leaves the risk taking to other parts of the world
- prevents untested novel techs to reach and impact the consumer
- reduces risk to a minimum for the EU public
- may decrease animal testing

CON‘s

- does not need, and use, sound science as a base
- works with the fears of the public
- not taking responsibilities and accepting liabilities
  (of agencies and registration authorities as well)
- innovation?

Threat or Chance: "the pipeline is drying up"*

- Phenomenon observed already for some time
- New techs can help filling it, but it has to be accepted that they need to be further researched and developed, also for the use in alternative methods
- New techs need novel approaches, these might help foster the introduction of new thinking at regulatory agencies
- Who is taking the lead?
  EU Commission and its Framework Programmes?

*H. Koëter,
former OECD Principal Administrator, current acting EFSA Head

Implementation of Alternative Methods:

Is the source drying up?

„A co-ordinated and target aimed cooperation is needed between:

- governmental regulatory experts,
- academic scientists,
- experts from the regulated community, and
- experts from the animal welfare community

in order to provide the breeding ground for new ideas and approaches in hazard assessment as well as in validation, taking into account both animal and non-animal approaches and integration of both.“

Citation from: H. Koëter, OECD website, slide 24

Biotechnology:

Testing Example in Place?

- did the new technology help in testing its own products? In terms of developing alternatives?

- GMOs: developing regulations in a novel technology area (e.g. food, feed and fibers)

Safety Assessment of GMOs

Approach	For Proteins	US	EU
• **Literature**	• Information on the organism source of the gene (toxic or allergenic source?)	T	✓
• **in vitro**	• Potential horizontal gene transfer to bacterial or mammalian cells	T	✓

• **in silico**	• Potential homology to known allergens or toxins
	  • overall amino acid sequence homology search with known allergens/toxins (80 aa)
	  • Epitope homology search with known allergens (8 aa)
		T	✓

• **in vitro**	• Protein stability
	  • digestibility in human simulated gastric fluid
	  • digestibility in human simulated intestinal fluid
	  • heat stability (60°C – 90°C)
		T	✓

	• Serum screening from allergic patients when suspicion of allergy	T	T

T = triggered
✓= Definitive requirement

Safety Assessment of GMOs in vivo

For Proteins (in vivo)

	US	EU
• Animal models to detect potential allergens (Brown Norway rat etc: INDIA)	T	T
• Acute oral toxicity studies in mice (OECD TG420 derived)	T	T

For Crop (in vivo)

• Subchronic rodent toxicity (CHINA, KOREA)	T	T
• Broiler chicken feeding study	T	T
• Pig/dairy cow feeding study	T	T
• Rabbit/goat feeding study (INDIA)	T	T
• Salmon feeding study (NORWAY)	T	T

T = triggered

Nanotechnology: Testing Example in Place?

- Toxicological Evaluation of Nanoscale Materials

„Approach
… and the logistics related to evaluating potential adverse effects of these materials in existing animal and in vitro-based toxicology models.

Source: US Material Toxicology Program

- „ The importance of Using Rodents in the Nanomedical Research“

Source: Feneque, J. (2005)
www.nanotsunami.com

Chances:

Toxicological Highlight

„In vitro Cytotoxicity of Nanoparticles in Mammalian Germ-Line Stem Cell“

…the full potential of alternative approaches in toxicological risk assessment has yet to be fully realized.“

Source: Vinardell, M.P. (2005)
Toxicological Sciences 88, 285-286

Nanosciences and its Convergence with other Technologies

New Golden Age or Apocalypse?

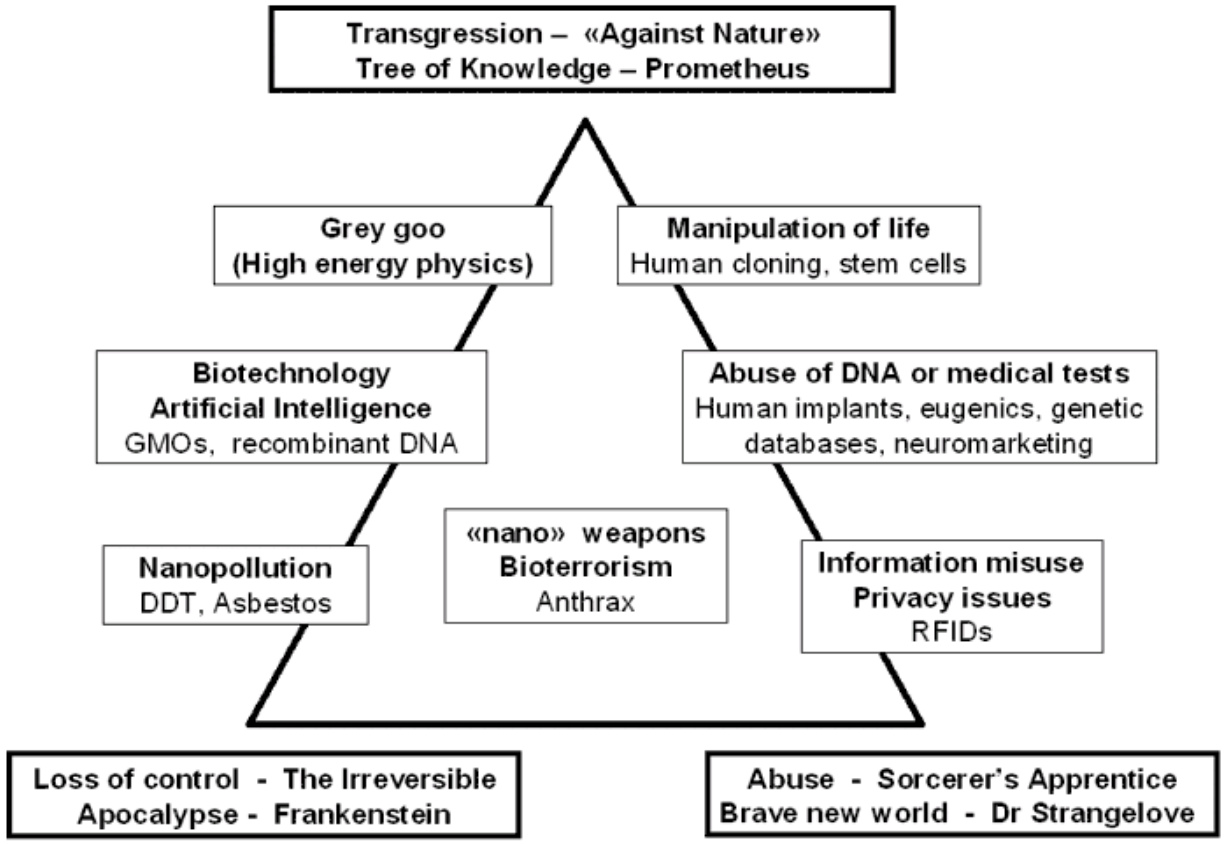
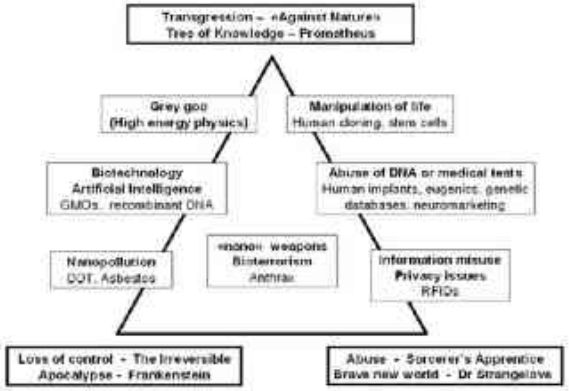


Figure 1: The three corner of the triangle represent the basic fears as discussed in Section 4. The rectangles on the corners represent the position of fears resulting from various new technologies (nanotechnologies including their convergence with other disciplines) regardless of how realistic they are. Some examples of already existing or past issues are included.

Nanosciences and its Convergence with other Technologies

New Golden Age or Apocalypse?



„The loss of control: new products“

Source:
Laurent, L., Petit, J.C.
HYLE Int.J.f.Philosophy of Chemistry
2005, 11, 45-76

„The micro- and nano-fabricated devices described only represent a small fraction of this rapidly growing toolbox available to the toxicologist.“

Micro- and Nano Biotechnologies
Chances for Toxicological Applications

Technology	Sensititvity	Toxicological Application
-Micropipet aspiration	-Single cell	-Effects on membrane viscoelasticity, function
-Electric cell impedance sensor	-Single cell	-Effects on membrane chemotaxis and cell attachment
-Traction force microscopy	-Single focal adhesion	-Effects on cell attachment and movement
-Surface plasmon resonance	-fm. antigen	-Effects on protein expression and cell function
-Grating coupled surface plasmon resonance	-nm. Antigen	-Effects on protein expression and cell function
-Laser capture microdissection	-Single cell	-Effects on cell and tissue function
-Biosensors: molecular whole cell whole organ/tissue		-Detection of pathogen, toxicant or biohazard presence

Source:
Shrinking the Biologic World – Nanobiotechnologies for Toxicology
Zieziulewicz, T.J. et al, 2003; Toxicological Sciences 74, 235-244

Citations

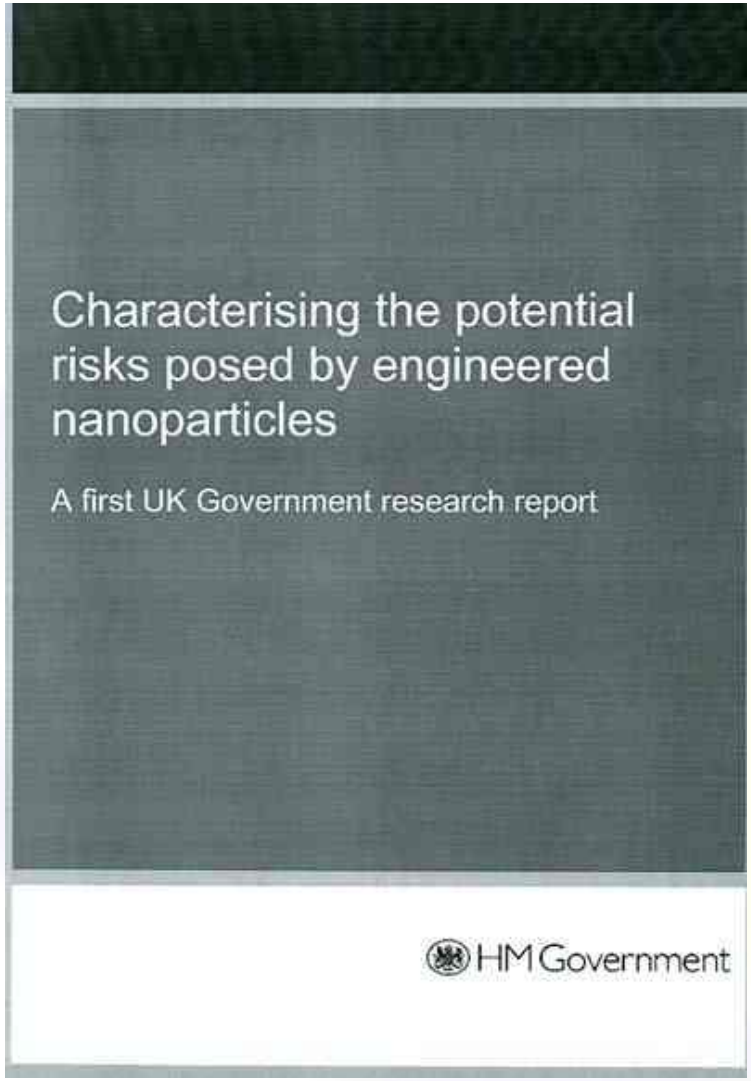
- Safety and Risks of Nanotechnology
  Lucerne, April 20-21, 2004

  - „In vitro studies in cell cultures have to determine the effects of nanoparticles on cell structure, function and interaction.
  - Evidence has to be proven in animal models by different application e.g. skin contact, inhalation, ingestion, injection.“

Conclusions of a Workshop:
Human Health and Nanobio-technology, Prof. Schapoval

- „Nanotech Meets the FDA: A Success Story about the first Nanoparticulate Drugs Approved by the FDA“

Till, M.C. et al.,
Nanotechnology Law Business
Feb 2, 2005



- EU Member States are following
- CEFIC Workshop, Barcelona, 2005

Hypothesis:

THREAT

- new techs require more testing of whole organism in vivo
- take too long to be used for alternatives
- excuse not to pursue other development
- not easy to regulate

or **CHANCE**

- follow and pursue new/novel developments
- basic research with applications in alternative method development needed
- the European competitiveness has impact on others (ICH, OECD,…)
- awareness fostered
- early on alternatives available

Conclusions

- As the source is drying up, we just cannot risk to overlook early signals (still need for esi ecopa Science Initiative !)

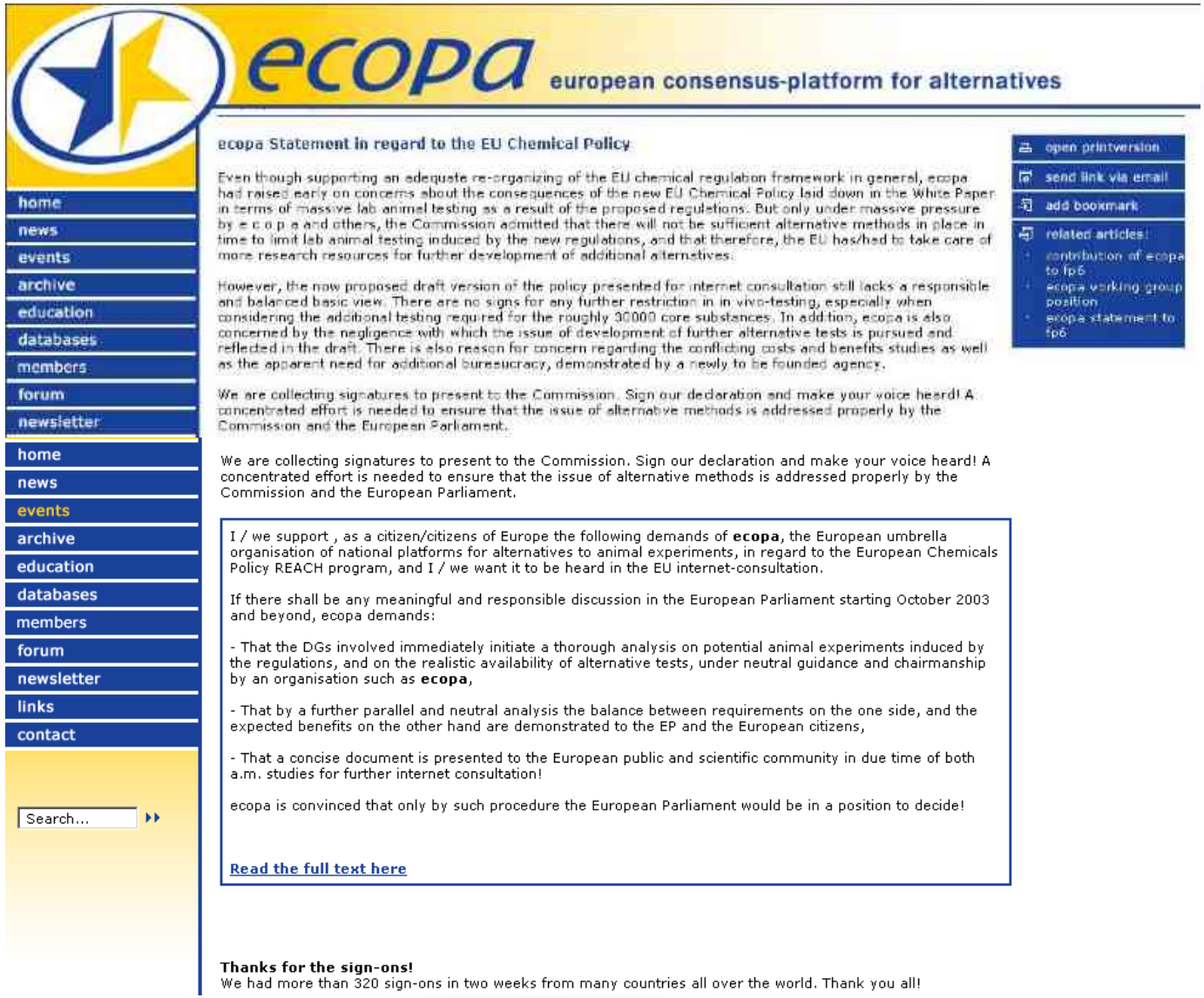
- It is detrimental (also for the EU being competitive) to only develop and simply validate „the same old stuff“ – make use of our biotech SME industry!

- Alternative method development has to go in parallel with the evolution of new techs (otherwise there remains in vivo-testing)

Reference made to "Alternative Methods" in European Regulations

No. Of Directive	Subject	Reference to Alternative
2003/81/EC	Medical Products for human use	**no**, ref to 86/609/EEC in body *
1999/45/EC	Dangerous Preparations	**no**, ref to 86/609/EEC in preamble and body
Reg. 2004/684/EC	Detergents	**no**, ref to 86/609/EEC in annex 1
76/768/EEC	Cosmetic Products	specific case: realism lost?
89/107/EEC	Food Additives (for human consumption)	**no**, **no** ref to 86/609/EEC in body
91/414/EEC	Plant Protection Products	**no**, ref to 86/609/EEC in preamble and body
93/42/EEC	Medical Devices	**no**, ref to 86/609/EEC in preamble and body
98/8/EC	Biocides	**no**, ref to 86/609/EEC in preamble and body

*under the heading „non clinical overview"



ecopa european consensus-platform for alternatives

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ecopa Statement in regard to the EU Chemical Policy

Even though supporting an adequate re-organizing of the EU chemical regulation framework in general, ecopa had raised early on concerns about the consequences of the new EU Chemical Policy laid down in the White Paper in terms of massive lab animal testing as a result of the proposed regulations. But only under massive pressure by e c o p a and others, the Commission admitted that there will not be sufficient alternative methods in place in time to limit lab animal testing induced by the new regulations, and that therefore, the EU has/had to take care of more research resources for further development of additional alternatives.

However, the now proposed draft version of the policy presented for internet consultation still lacks a responsible and balanced basic view. There are no signs for any further restriction in in vivo-testing, especially when considering the additional testing required for the roughly 30000 core substances. In addition, ecopa is also concerned by the negligence with which the issue of development of further alternative tests is pursued and reflected in the draft. There is also reason for concern regarding the conflicting costs and benefits studies as well as the apparent need for additional bureaucracy, demonstrated by a newly to be founded agency.

We are collecting signatures to present to the Commission. Sign our declaration and make your voice heard! A concentrated effort is needed to ensure that the issue of alternative methods is addressed properly by the Commission and the European Parliament.

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related articles:
- contribution of ecopa to fp6
- ecopa working group position
- ecopa statement to fp6

We are collecting signatures to present to the Commission. Sign our declaration and make your voice heard! A concentrated effort is needed to ensure that the issue of alternative methods is addressed properly by the Commission and the European Parliament.

I / we support , as a citizen/citizens of Europe the following demands of **ecopa**, the European umbrella organisation of national platforms for alternatives to animal experiments, in regard to the European Chemicals Policy REACH program, and I / we want it to be heard in the EU internet-consultation.

If there shall be any meaningful and responsible discussion in the European Parliament starting October 2003 and beyond, ecopa demands:

- That the DGs involved immediately initiate a thorough analysis on potential animal experiments induced by the regulations, and on the realistic availability of alternative tests, under neutral guidance and chairmanship by an organisation such as **ecopa**,

- That by a further parallel and neutral analysis the balance between requirements on the one side, and the expected benefits on the other hand are demonstrated to the EP and the European citizens,

- That a concise document is presented to the European public and scientific community in due time of both a.m. studies for further internet consultation!

ecopa is convinced that only by such procedure the European Parliament would be in a position to decide!

Read the full text here

Thanks for the sign-ons!
We had more than 320 sign-ons in two weeks from many countries all over the world. Thank you all!