Ecopa: state-of-the-art and future

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Abstract

Ecopa, the European Consensus Platform on Alternatives, is an International Not-For-Profit organization, based in Belgium and complying with Belgium law. It is the only quadripartite organization at EU level, which is promoting the 3Rs at the European level. Ecopa brings together National Consensus Platforms on alternative methods. Consensus means that all parties concerned are represented, including animal welfare, industry, academia and governmental institutions. Ecopa actually counts 14 Member State (or future Member State) National Platforms (8 full members, platforms of Austria, Belgium, Finland, Germany, The Netherlands, Spain, Switzerland and United Kingdom and 6 associate members being Czech Republic, Denmark, Italy, Norway, Poland and Sweden) and has 3 working groups.

The fields of interest of these working groups change according to the needs and were until now concerned with (i) the 6th Framework Programme of the EC for Research, Technological Development and Demonstration Activities, (ii) the EC White Paper Strategy for a Future EU Chemicals Policy and (iii) the formation & educational programmes on alternative methods.

Ecopa is thus uniquely placed and has huge expertise to offer to the debate around scientific and politically-linked topics. It has to be considered a key stakeholder by the European Commission and Parliament. (http://ecopa.vub.ac.be).

Key words: national platforms, consensus, alternative methods, 3Rs..

Introduction

Ecopa stands for the European consensus Platform on Alternatives. It is a quadripartite organization at the EU level promoting the 3Rs strategy for the replacement, reduction and refinement of experimental animals in regulatory testing and research. Ecopa brings together all national consensus platforms on alternative methods, in which the four parties concerned are represented, being animal welfare, industry, academia and governmental institutions.

The idea for its creation goes back to an ECVAM meeting in 1999 to which representatives of the national platforms, groups or centres existing in Europe and working around alternative methods, were invited. The situation, at that time, with respect to the existence and functioning of national centres was so heterogeneous that during the 3rd World Congress on Alternatives and Animal Use in the Life Sciences, a Workshop was held to discuss the existence and necessity of national platforms (1).

The idea was introduced to stimulate the formation of quadripartite platforms (consensus platforms) at the national level and to bring these together in quadripartite organization at the EU level.

Since then, two ecopa Workshops have been held in Brussels. During the first one (October 2000), the implementation of ecopa at the EU level was discussed, its objectives and tasks were defined and its preliminary structure was proposed (2).

The second Workshop (October 2001) was focussed on the important topic of the EC White Paper Strategy for a Future EU Chemicals Policy (3) and its implementations for animal welfare and the use of alternative methods.

During the 3rd World Congress on Alternatives and Animal use in the Life Sciences, held in Bologna in 1999, the basis was formed for the creation of ecopa, the European Consensus Platform on Alternatives (1).

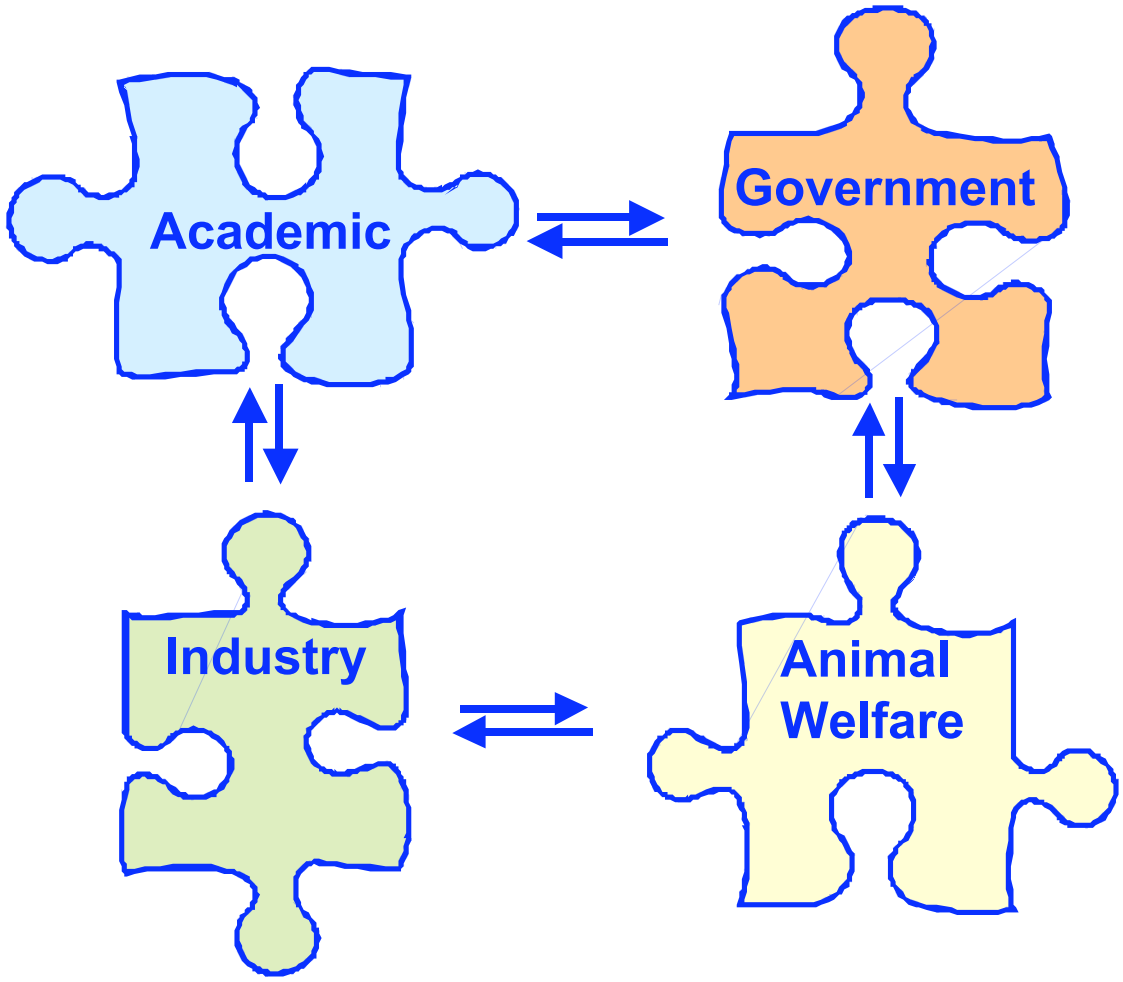
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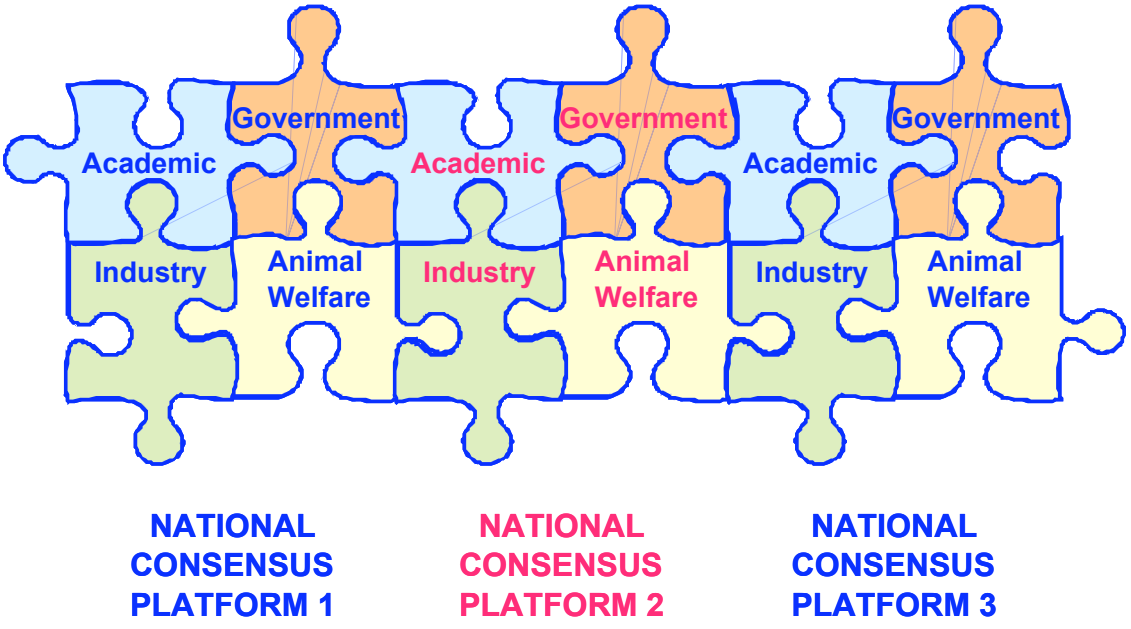
Figure 1b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Discussion

2.1. Actual status of ecopa

Acceptation and publication of the statutes, will provide ecopa with the status of an International Not-for-Profit Organization based in Belgium and complying with the Belgian Law (4). Starting at Bologna in 1999 with only 3 national platforms (B, D, NL), to-day already eight full members and six associate members participate.

Present as full members are:

Austria (W. Pfaller), Belgium (P. Beaufays), Finland (R. Salmi), Germany (B. Garthoff), The Netherlands (W. De Leeuw), Spain (J. Castell), Switzerland (P. Maier), United Kingdom (K. Boyd). The six associate members include Czech Republic (D. Jírová), Denmark (O. Svendsen), Italy (A. Stammati), Norway (A. Smith), Poland (M. Stepnik) and Sweden (K. Gabrielson), of which Italy and the Czech Republic are doing a lot of efforts in order to comply with all criteria of a consensus platform in order to become a full member of ecopa.

Actually, three working groups are functioning of which the fields of interest can be changed according to the most urgent needs in the field of alternative research and testing. Until now their responsibilities were as follows:

- The first group, headed by V. Rogiers (B), actually focused on the 6th Framework Programme (FP6) in Europe and the possibility to get European funding for research into and development of alternative methods. This group also coordinated the general follow-up of statutes, website, workshops, administrative tasks until the official elections of the Board Members during the 3rd Ecopa Workshop (November 2002). This working group was invited at the round table discussion of the Commission during the "Conference on the state of the art of research - replacement, reduction and refinement - alternatives to animal experimentation and testing", jointly organized by DG Research and DG Joint Research Centre (JRC) (5).

- The second group, headed by K. Gabrielson (S), worked around the issue of animal testing and the implementation of alternative methods with respect to the EU White Paper Strategy for a Future EU Chemicals Policy (3). A research proposal consisting of 16 different projects on the development of alternative methods has been drafted coming from ecopa members and has been forwarded to the "expression of interest" call of FP6. These proposals have been taken up in the website of the EC at http://www.cordis.lu/en/home.html/
- The third group is headed by J. van der Valk (NL) and concentrates on developing information and education programmes on alternative methods.
- In Table I, an overview of the participating members is given. Efforts have been done to equilibrate the representation of the 4 parties concerned (Academia, Industry, Government and Animal Welfare).

2.2. What have ecopa Working groups realised until now?

2.2.1. Position of ecopa with respect to the EU policy on alternative methods.

In order to understand the realisations of the ecopa working groups 1 and 2, we need first to explain the starting point of the activities of both workgroups when founded during the second ecopa Workshops (October 2001) and the position that ecopa was taking with respect to the EU policy on alternative methods.

There were five important issues that needed to be considered carefully:

(a) The existing validated alternative methods and the lacking candidates for validation;

(b) The EU White Paper Strategy for a Future Chemicals Policy (3);

(c) ECVAMs vision on the future;

(d) The coming 7th Amendment of the EU;

(e) The 6th Framework Programme draft of the EC for Research, Technological Development and Demonstration Activities.

Let us consider each in some more detail.

(a) The existing validated alternative methods and the lacking candidates for validation.

The number of validated 3R methods available for the practical application in regulatory testing and risk assessment of chemical substances was and is limited (6).

Alternative methods currently available are:

- 4 formally validated 3R methods according to the validation strategy of ECVAM (6-8), namely 3 corrosivity tests (the rat skin transcutaneous electrical resistance or TER; Episkin® and Epiderm®, two commercially available human epidermis constructs) and 1 phototoxicity test, the 3T3 neutral red uptake or 3T3 NRU-phototoxicity test. They are taken up in Annex V of the Dangerous Substances legislation in Europe (9).
- 6 methods accepted by ESAC (European Scientific Advisory Committee) advising ECVAM (European Centre for the validation of Alternative Methods), but not (yet) taken up in the EU legislation. They consist of: the murine local lymph node assay (LLNA) for skin sensitisation; the *in vitro* percutaneous absorption test; Corrositex®, an additional corrosivity test only suitable for testing acids and bases; and three embryotoxicity tests (the whole embryo culture test or WEC; the micromass test or MM, and the embryonic stem cell test or ECT).
- *In vitro* genotoxicity testing as commonly used in industry for regulatory purposes and recognized by the OECD (Organisation For Economic Co-operation and Development).
- For acute toxicity testing, 3 refinement tests have been validated (externally, not within old ECVAM), and accepted at the OECD and EU level, namely the fixed dose procedure (OECD n° 420, B.1bis in Annex V, the acute toxicity class procedure (OECD n° 423, B.1tris in Annex V). and the up and down procedure (OECD n° 425), not yet an equivalent in Annex V to Directive 67/458/EEC). They replace the classical LD_{50} test (OECD n° 401).

- For skin irritation and eye irritation, validation studies are running but they have not yet provided replacement tests applicable across the full range of chemical substances. For acute lethal toxicity (oral), a validation study of a basal cytotoxicity test is initiated by ICCVAM (Inter-agency Co-ordinating Committee on the Validation of Alternative methods) and ECVAM (10).

For the testing of biokinetic endpoints, target organ toxicity, systemic toxicity, repeat-dose toxicity, non-genotoxic carcinogenicity, reproductive toxicity, acute (dermal, inhalation) lethal toxicity, all of strategic importance for the regulatory testing of chemicals according to the actual Directive 67/548/EEC, no validated alternative methods are available yet (table II). On the contrary, the *in vivo* tests today consume a high number of animals.

(b) The EU White Paper Strategy for a Future Chemicals Policy (3)

More than 100.000 substances existed on the European market before September 1981 and were taken up on the EINECS (European Inventory of Existing Commercial Chemical Substances) list. Of these only a limited number of toxicological data are available, often of a rather poor scientific quality.

About 3000 new substances are present on the ELINCS (European List of Notified Chemical Substances) list and these have been tested according to Directive 67/548/EEC). Knowledge is thus lacking for about 99% of the chemicals actually present on the EU market. The risk assessment process of studying each chemical, case by case, is a slow and expensive process and most resources to-day are used for new chemicals.

The EU policy proposed to introduce the REACH system (Registration, Evaluation, Authorisation) with a priority for CMRs (carcinogenic, mutagenic, reproduction toxic substances), POPs (persistent organic polluents), PBTs (persistent, bioaccumulative and toxic substances) and VPVBs (very persistent and very bioaccumulative substances).

Roughly, about 30.000 existing chemicals, produced in amounts higher than 1 tonne/year would be involved.

The goal would be to collect *in vitro* data for the molecules produced in amounts between 1-10 tonnes/year and *in vitro & in vivo* data for those in amounts more than 10 tonnes/year.

According to the source used (11), the number of animals involved has been estimated to range from 9.6 to 12.8 million with a total cost ranging between 2.1 and 8.68 billion euro.

(c) ECVAMs vision on the future.

ECVAM had proposed an optimistic strategy plan for the future development and validation of alternative methods (10). It was, however, not evident to accept the statement in the report that within the next five years, alternative methods, will be available for most if not all endpoints (10). From experience of the past, we know that pre-validation and validation are time-consuming exercises. It may take up to 8 years before a method is validated and officially incorporated into the EU legislation. For most of the toxicological tests, mentioned in table II (chronic toxicity, systemic toxicity, reproductive toxicity), appropriate methods have not yet been developed. Consequently such *in vitro* tests are today not present in the pipeline of pre-validation/validation. It therefore seems rather impossible to have them available and fully validated within 5 years, even if the whole process can be speeded up importantly because of the experience gained from previous exercises.

(d) The coming 7th Amendment of the EU Cosmetic Legislation

In Europe, the number of animals used for testing of cosmetic ingredients and finished products is relatively small in comparison with other fields of consumption e.g. drugs, pesticides, chemicals.

The Sixth (12) and the proposal for a Seventh Amendment (13), however, imply under well-defined conditions, an animal testing ban and a marketing ban of cosmetic ingredients and finished products. Consequently, the availability and application of alternative methods for testing cosmetic products and their ingredients become essential.

(e) The 6th Framework Programme draft of the EC for Research, Technological Development and Demonstration Activities.

Basically, the 6th Framework Programme (FP6) will determine the research for the period 2002 to 2006 in Europe (14).

However, in the Common Position of FP6 (draft versions) no specific key action on alternative methods was proposed. In addition, nearly no mentioning of alternative methods was done throughout the whole programme text. It was stated that Integrated Projects and Networks of Excellence will contribute to strengthening European competitiveness and help solve major societal problems by mobilizing a critical mass of research and development resources and skills existing in Europe.

Although the time frame of the white Paper and FP6 nearly was the same, no mention was been done of the specific problem of the increased animal use with respect to the EU policy on chemicals and the development of alternative methods, urgently needed for the implementation of both the chemicals strategy and the new cosmetic legislation.

2.2.2. Actions taken by Ecopa Working groups 1 and 2

Because of the problems raised under 2.2.1., the ecopa Working groups therefore have issued a common position statement on the White Paper (in relation to the Sixth Framework programme). Based on the huge expertise that the quadripartite organization of ecopa offers, strong practical and realistic recommendations were forwarded to the European Commission and Parliament.

This statement was sent to the different EU services concerned, MEPs, politicians, pressure groups, non governmental organizations, representatives of national platforms, etc. and is present on the ecopa website (2). Consequently, a Conference was organized by the Commission (DG Research and DG Joint Research Centre) with the different stakeholders including ecopa (5) to discuss the state-of-the-art of the 3Rs in research and to see whether

and where problems in the FP6 were present. Representatives of the ecopa Working groups 1 and 2 played a key role in the discussions. Finally, the Commission promised that an entry for research projects on alternatives in the context of the urgent needs, mentioned above, would become available under scientific support to Community policies (generally known as priority 8).

In September 2002 rewriting of a part of the FP6 text was indeed carried out, and among the scientists invited by the Commission to guide the whole exercise, a representative of the ecopa Working groups was present. This participation turned out to be of critical importance. Thus all efforts resulted in the fact that alternative methods are now among the key actions of the FP6. This opens possibilities for scientists working on the development of alternative methods, which was the immediate and direct goal of Working groups 1 and 2.

Also, when the Commission initiated a call of interest in June 2002, in the research area of genomics and proteomics, Working group 1 entered 16 research proposals that were collected from the different ecopa member countries. They are present on EC website at http://www.cordis.lu/en/home.html/ and are summarized here in table III.

2.3. Coming initiative of ecopa

The paths towards regulatory acceptance, after the successful prevalidation and validation of alternative methods, are multiple and time consuming. It is therefore quite urgent to analyze the difficulties that exist in introducing and implementing alternatives into national, European and supra-national (e.g. OECD) guidelines and to look for ways to speed up this process.

It is on this topic that the 3rd Ecopa Workshop will be organized (November 8-10, 2002) in Brussels, in collaboration with the OECD. Programme details are present on the ecopa website (2).

During the Workshop new tasks in the context of the speeding up process will be identified for Workgroups 1 and 2. In addition, statutes will be finalized an ecopa will be officially founded as a non-governmental organization (ngo).

Conclusions

Ecopa is now a well-organized and structured organization. It is unique, since it is the only quadripartite organization at the EU level promoting the 3Rs strategy for the replacement, reduction and refinement of experimental animals in regulatory testing and research.

Ecopa comprises 14 Member State (or future Member State) National Consensus Platforms representing animal welfare groups, academia, industry and government.

Through its members it has an important scientific and technical expertise to offer to the debate of current problems with respect to the use of experimental animals and the development of alternative methods.

Ecopa has to be considered a key stakeholder by the European Commission and Parliament in issues as they are present today. Ecopa will make scientifically and politically inspired statements and recommendations and will organize scientific /political activities in order to stimulate and activate the development of alternative methods in the EU and to speed up their introduction and implementation into national, European and supra-national guidelines.

Acknowledgements

The discussion with representatives of the different ecopa working groups were highly appreciated.

References

(1) Rogiers V. (2000). The role of national platforms. In *Progress in the Reduction, Refinement and Replacement of animal Experimentation*, pp 1713-1718. Amsterdam: Elsevier Science BV.

(2) Ecopa website: http://ecopa.vub.ac.be

(3) Strategy for Future EU Chemicals Policy, website http://www.europa.eu.int/comm/environment/chemicals/whitepaper.htm

(4) Anonymous (2000). Association Internationale a but philanthropique, réligieux, scientifique, artistique ou pédagogique, Loi du 25 octobre 1919, modifiée par la loi du 6 décembre 1954, modifiée par la loi du 30 juin 2000.

(5) Conference on the State-of-the-Art of Research, Replacement, Reduction and Refinement Alternatives to Animal Experimentation and Testing. Brussels, 9-10 July 2002, website http://europa.eu.int/comm/research/info/conferences/rrr/rrr_en.html

(6) Liebsch, M. and Spielman, H. (2002). Currently available *in vitro* methods used in the regulatory toxicology. *Toxicology Letters* **127**, 127-134.

(7) Balls, M., Blaauboer, B.J., Fentem, J.H., Bruner, L., Combes, R.D., Ekwall, B., Fielder, R.J., Guillouzo, A., Lewis, R.W., Lovell, D.P., Reinhardt, C.A., Repetto, G., Sladowski, D., Spielmann, H., and Zucco, F. (1995). Practical aspects of the validation of toxicity test procedures. The report and recommendations of ECVAM workshop 5. *Alternatives To Laboratory Animals* **23**, 129-147.

(8) Worth, A. and Balls, M. (2001). The importance of the prediction model in the development and validation of alternative tests. *Alternatives To Laboratory Animals (ATLA)* **29**, 135-143.

(9) Anonymous (1967). Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Official Journal of the European Communities* **196**, 16-08-1967.

(10) Worth, A. and Balls, M. (2002). Alternative (non-animal) methods for chemicals testing: current status and future prospects. A report prepared by ECVAM and the ECVAM

working group on chemicals. *Alternatives To Laboratory Animals*, (ATLA) 30, suppl. 1, pp. 125

(11) Botham, K., Green, E., Holmes, P. and Harrison, P. (2001). Testing requirements for proposals under the EC White Paper "Strategy for a Future Chemicals Policy". An institute for Environment and Health report for the department of the Environment, Transport and Regions, website http://www.le.ac.uk/ieh/publications/publications.html

(12) Anonymous (1993). Council Directive 93/35/EEC of 14 June 1993 amending for the sixth time Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products. *Official Journal of the European Communities* **L151/32-36**, 23-06-1993.

(13) Anonymous (2002). Proposal for a European Parliament and Council Directive amending for the seventh time Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products [COM(2000)189 – C5-0244:2000 – 20000/0077(COD)]. *Official Journal of the European Communities* **C21E, 0088-0103,** 24-01-2002.

(14) Anonymous (2002). Common Position adopted by the Council with a view to the adoption of a Decision of the European Parliament and the Council concerning the Sixth Framework Programme of the European Community for Research, Technological Development and Demonstration Activities, contributing to the creation of the European Research Area and to innovation (2002 - 2006), website ftp://ftp.cordis.lu/pub/rtd2002/docs/fp6_council_0102.pdf

Table I: Overview of the topics and members of the ecopa working groups

Ac: Academic; An: Animal Welfare; Go: Governmental institutions; I: Industry.

Working group	Topics	Members
1	° Sixth Framework Programme ° General follow-up of ecopa	J. Castell (E, Ac) K. Gabrielson (S, An) B. Garthoff (D, I) K. Pelkonen (F, Go) P. Maier (CH, An + I) V. Rogiers (B, Ac) A. van Iersel (NL, Go)
2	EU White Paper on Chemicals	L. Bansil (UK, I) K. Gabrielson (S, An) M. Kayser (D, I) W. Pfaller (A, Ac) R. Salmi (F, An) H. Spielman (D, Go) M. Weber (I, I)
3	Information & education programmes	J. van der Valk (NL, An) A. Smith (N, Ac)

Table II: Prospects for the availability of validated alternative methods in the near future

NOT AVAILABLE	AVAILABLE
- PHOTOALLERGY - SUBACUTE TOXICITY - CHRONIC TOXICITY` - REPRODUCTIVE TOXICITY - TARGET ORGAN & SYSTEMIC TOXICITY - BIOKINETICS - NON GENOTOXIC CARCINOGENICITY	- ACUTE ORAL TOXICITY - SKIN IRRITATION - PHOTOTOXICITY - OCULAR IRRITATION - SKIN SENSITISATION - EMBRYOTOXICITY

(http://minf.vub.ac.be/~fafy/ecopa)