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Ecopa: actual status and plans

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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 3R-Alternatives at the European level. Ecopa brings together National Consensus Platforms on alternative methods. Consensus means that all parties concerned are represented: animal welfare, industry, academia and governmental institutions. Ecopa actually counts 14 National Platforms of Member States (or future Member States), (8 full members, platforms of Austria, Belgium, Finland, Germany, The Netherlands, Spain, Switzerland and United Kingdom and six associate members being Czech Republic, Denmark, Italy, Norway, Poland and Sweden) and has three 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) or http://ecopa.tsx.org).

Keywords: National platforms; Consensus; Alternative methods; 3Rs

1. Introduction

Ecopa stands for the European Consensus Platform on 3R-Alternatives. It is a quadripartite organisation 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 1997 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 (Rogiers, 2000).

The idea was introduced to stimulate the formation of quadripartite platforms (consensus platforms) at the national level and to bring these together in a quadripartite organisation at the EU level (Fig. 1a,b).

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 (Ecopa).

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

2. Discussion

2.1. Actual status of ecopa

Acceptation and publication of the statutes, will provide ecopa with the status of an International Not-for-

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Profit Organization based in Belgium and complying with the Belgian Law (Anonymous, 2000). Starting at Bologna in 1999 with only three national platforms (B, D, NL), today 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 (W. Wasowicz, replaced by 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), 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 (Conference on the state-of-the-art of research, replacement, reduction and refinement alternatives to animal experimentation and testing, 2002).
- 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 (Strategy for Future EU Chemicals Policy). 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 http://www.cordis.lu/fp6/eoi-analysis.htm#pdf.
- The third group just started and is headed by J. van der Valk (NL). It will concentrate on developing information and education programmes on alternative methods.

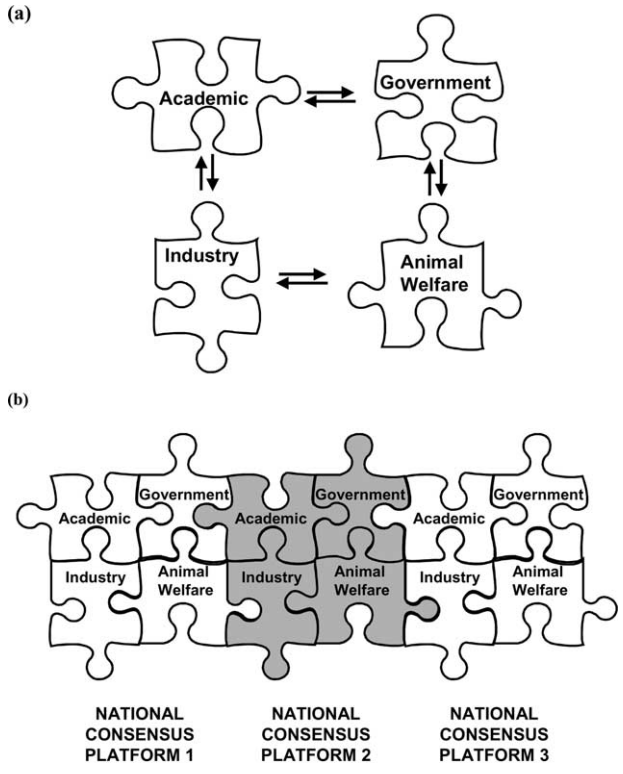

Fig. 1. (a) National consensus platforms as quadripartite organisations (b) forming the basis of the European organisation Ecopa.

In Table 1, an overview of the participating members is given. Efforts have been done to equilibrate the representation of the four parties concerned (Academia, Industry, Government and Animal Welfare).

Table 1
Overview of the topics and members of the ecopa working groups

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)

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

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 Workshop (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 (Strategy for future EU chemicals policy);
c. ECVAMs vision on the future;
d. The coming 7th Amendment of the EU Cosmetic Legislation;
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 (Liebsch and Spielman, 2002).

Alternative methods currently available are:

- Four formally validated 3R methods according to the validation strategy of ECVAM (Botham et al., 2001; Conference on the state-of-the art of research, replacement, reduction and refinement alternatives to animal experimentation and testing, 2002; Ecopa), namely three 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 (Council Directive 67/548/EEC).
- Six methods accepted by ESAC (ECVAM 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 ECVAM), and accepted at the OECD and EU level, namely the fixed dose procedure (OECD no. 420, B.1bis in Annex V to Directive 67/458/EEC), the acute toxicity class procedure (OECD no. 423, B.1tris in Annex V) and the up and down procedure (OECD no. 425, not yet an equivalent in Annex V to Directive 67/458/EEC). They replace the classical LD_{50} test (OECD no. 401).
- For skin and eye irritation, validation studies are running but they have not yet provided replacement tests that are 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 (Interagency Co-ordinating Committee on the Validation of Alternative methods) and ECVAM (Worth and Balls, 2002).

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 2). On the contrary, the in vivo tests still in use today are those that consume the highest numbers of animals.

Table 2
Prospects for the availability of validated alternative methods in the near future

Not available	Probably available
acute (inhalation,dermal) toxicity	acute oral toxicity
	skin irritation
photoallergy	phototoxicity
subacute toxicity	ocular irritation
chronic toxicity	skin sensitisation
reproductive toxicity	embryotoxicity
target organ & systemic toxicity	
biokinetics	
non genotoxic carcinogenicity	

(b) The EU White Paper Strategy for a Future Chemicals Policy (Botham et al., 2001)

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 available resources to-day are mostly 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 and in vivo data for those in amounts more than 10 tonnes/year.

According to the source used (Botham et al., 2001), 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 recently did propose an optimistic strategy plan for the future development and validation of alternative methods (Worth and Balls, 2002). It is, however, not evident to hope that within the next five years, alternative methods, would be available for most if not all endpoints. From experience of the past, we know that good pre-validation and validation studies are time-consuming exercises. They may take up to 6–8 years before a method is validated and officially incorporated into the EU legislation. For most of the toxicological tests, mentioned in Table 2 (chronic toxicity, systemic toxicity, reproductive toxicity,. . ..), appropriate alternative methods have not yet been developed. Consequently they are not present in the pipeline of prevalidation/validation. It therefore seems rather impossible to have them available and fully validated within five years, even if the whole process could be speeded up importantly because of experience gained in the previous pre- and validation studies.

(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 Amendment (Council Directive 93/35/EEC) and the proposal for a Seventh Amendment (Anonymous, 2002b), 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 (Anonymous, 2002a).

However, in the Common Position of FP6 (draft versions, Anonymous, 2002a) 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 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.

2.3. *Actions taken by Ecopa Working groups 1 and 2*

Because of the problems raised above, the ecopa Working groups 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 (Ecopa).

Consequently, a Conference was organized by the Commission (DG Research and DG Joint Research

Centre) with the different stakeholders including ecopa (Conference on the state-of-the-art of research, replacement, reduction and refinement alternatives to animal experimentation and testing, 2002) 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

Table 3
Research projects on alternative methods coming from ecopa member countries and entered as EoIs by Ecopa Working group 1

Author/affiliation	Topic
D. Jírová Ntl. Reference Center for Cosmetics, Ntl. Institute of Public Health, Praha, Czech Republic	Estimation of skin irritancy on the basis of cytotoxicity results
V. Rogiers Dpt. Toxicology, Vrije Universiteit Brussel, Belgium	Stable long-term culture models for different types of highly differentiated cells: strategic need in level 1 and level 2 testing of chemicals
H.S.E. Tähti University Medical School, Tampere, Finland	Stable long-term culture models for different types of highly differentiated cells: strategic need in level 1 and level 2 testing chemicals
C. Clemedson EDIT programme, Expertrådet AB, Sundbyberg, Sweden	Development of an In Vitro Battery for the Estimation of Acute Human Systemic Toxicity: The EDIT programme
H. Spielmann, Dr. A. Seiler ZEBET, BgVV, Berlin, Germany	The use of pluripotent cell culture models and highly differentiated cells to predict developmental toxicity
H.J. Ahr Dpt. Research Toxicology, Bayer AG, Wuppertal, Germany	Possible impact of toxicogenomics on the 3R
A. Forsby, R. Clothier Dpt. Neurochemistry and Neurotoxicology, Stockholm University, Sweden	Sensory innervation models for the estimation of compromising human corneal epithelial barrier function, as predictors of potential human mild eye irritation
B. Isomaa Dpt. Biology, Åbo Akademi University, Turku, Finland	Evaluation of the possibility to use in vitro tests to predict endocrine disrupting effects in vivo
P. Vihko Oulu University Hospital, Finland	Mass production of cells and recombinant proteins to develop models for testing compounds modulating sex hormone activity
G. Sponer SET, Mainz, Germany	Can the test on abnormal toxicity be deleted?
M. Stepnik Toxicology; The Nofer Institute of Occupational Medicine, Lodz, Poland	Developing the cellular microarrays for toxicity testing
B. J. Blaauboer Institute for Risk Assessment Sciences (IRAS), Div. of Toxicology, Utrecht University, Utrecht, The Netherlands	Novel strategies for risk assessment of compounds in the food chain: integration of data on physico-chemical properties, in vitro toxicity and biokinetic modelling.
W. Gubbels Section HEAD Existing Chemicals, NOTOX, 's-Hertogenbosch, The Netherlands	An Alternative Approach for the Safety Investigations on Existing Chemicals (Exploration of the 3-R-approach)
M. Cervinka Dpt. Medical Biology & Genetics, Charles University, Faculty of Medicine, Hradec Kralove, Czech Republic	Dynamic aspect of toxic response based on analysis of the behaviour (morphology, proliferation, cell death, etc.) of individual cells
Ph. Vanparys Johnson & Johnson Pharmaceutical Research and Development, a division of Janssen Pharmaceutica N.V., Beerse, Belgium	The need of positive control animals for routine *in* vivo micronucleus testing
J. Castell Dept. de Bioquimica, Fac. Medicina/Centro de Investigacion, Hospital Universitario Valencia, Spain	Toxicogenomics

the FP6. This opens possibilities for scientists working on the development of alternative methods, a result that 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 http://www.cordis.lu/fp6/eoi-analysis.htm#pdf and are summarized here in Table 3.

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 in this context that the 3rd Ecopa Workshop will be organized (November 9–10, 2002) in Brussels, in collaboration with the OECD. Programme details are present on the ecopa website (Ecopa).

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 and ecopa will be officially founded as a non-governmental organization (ngo).

4. 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

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