

ECOPA: The European Consensus Platform on Three Rs Alternatives

Vera Rogiers

Department of Toxicology, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium

E-mail: vrogiers@fafy.vub.ac.be

Summary — ECOPA, the European Consensus Platform on Alternatives, is an international not-for-profit organisation, based in Belgium and complying with Belgium law. It is the only quadripartite organisation that is promoting the Three Rs at the European level. ECOPA brings together the National Consensus Platforms on alternative methods in Europe. Consensus means that all parties concerned are represented, including animal welfare, industry, academia and governmental institutions. Ecopa actually comprises 14 Member State (or future Member State) National Platforms (eight full members: the platforms of Austria, Belgium, Finland, Germany, The Netherlands, Spain, Switzerland and the UK; and six associate members: the 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 actually are concerned with a) the Sixth Framework Programme of the European Commission (EC) for Research, Technological Development and Demonstration Activities, b) the EC *White Paper on a Strategy for a Future Chemicals Policy*, and c) the formation of educational programmes on alternative methods within the EU. 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. News and views of ECOPA can be found on the ECOPA website (<http://www.ecopa.tsx.org/>), which is regularly updated.

Key words: *alternative methods, consensus, in vitro methods, national platforms.*

Introduction

During the Third 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). Ecopa brings together all the national consensus platforms on alternative methods in Europe, in which the four concerned parties are represented: animal welfare, industry, academia and government institutions. Since then, two European workshops have been held in Brussels.

During the first workshop (October 2000), the implementation of ECOPA at the European Union (EU) level was discussed, its objectives and tasks were defined; and its preliminary structure was proposed (2).

The second workshop (October 2001) focused on the foundation of ECOPA and its statutes (2). The important topic of the European Commission (EC) *White Paper on a Strategy for a Future Chemicals Policy* (3) was discussed with all parties concerned and its implications for animal welfare and the use of alternative methods were analysed.

A third workshop is planned for November 2002, in Brussels, and will deal with the difficulties of introducing and implementing alternative methods into national, European and supra-national (e.g. the Organization for Economic Cooperation and Development [OECD]) guidelines.

Discussion

Actual status of ECOPA

The publication of the statutes, after the third workshop in November 2002, will provide ECOPA with the status of an international not-for-profit organisation, based in Belgium, and complying with the Belgian Law (4). Starting at Bologna, in 1999, with only three national platforms, Belgium, Germany and The Netherlands (B, D, NL), eight full members and six associate members already participate. Present as full members are: Austria (represented by W. Pfaller), Belgium (P. Beaufays), Finland (R. Salmi), Germany (B. Garthoff), The Netherlands (W. De Leeuw), Spain (J. Castell), Switzerland (P. Maier) and the United Kingdom (K. Boyd). The six associate members are the Czech Republic (D. Jírová), Denmark (O. Svendsen), Italy (A. Stammati), Norway (A. Smith), Poland (W. Wasowicz) and Sweden (K. Gabrielson).

Three working groups are functioning, and their respective fields of interest can be changed according to the most urgent needs in the field of alternative research and testing.

The first group, headed by V. Rogiers (B), focuses on the Sixth Framework Programme (FP6) in Europe and the possibility of getting European funding for the development of alternative methods. This group also coordinates the general follow-up of

statutes, website, workshops and administrative tasks until the official elections during the third workshop of the Executive Committee and Board Members. This working group was invited to attend 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 organised by DG Research and DG Joint Research Centre (JRC) (5).

The second group, headed by K. Gabrielson, Sweden (S), works around the issue of animal testing and the implementation of alternative methods with respect to the EU *White Paper on a Strategy for a Future Chemicals Policy* (3). A research project around this theme has been drafted with the collaboration of most of the ECOPA members and has been forwarded to the “expression of interest” call of FP6.

The third group is headed by J. van der Valk (NL) and concentrates on developing information and education programmes on alternative methods.

In Table 1, an overview of the participating members is given.

Position of ECOPA with respect to the actual EU policy and the availability of validated alternative methods

Validated alternative methods

At present, the number of validated Three Rs methods available for practical application in regulatory

testing and risk assessment of chemical substances is limited (6).

Alternative methods currently available are:

- Four formally validated Three Rs methods according to the validation strategy of the European Centre for the Validation of Alternative Methods (ECVAM [6–8]), namely, three corrosivity tests (the rat skin transcutaneous electrical resistance or TER; EPISKIN™ and EpiDerm™, two commercially available human epidermis constructs), and one phototoxicity test, the 3T3 neutral red uptake phototoxicity test. They are taken up in Annex V of the Dangerous Substances legislation in Europe (9).
- Six methods have been accepted by the ECVAM Scientific Advisory Committee (ESAC), which advises ECVAM, but not (yet) taken up into EU legislation. They are: 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 recognised by the OECD.

For skin irritation and eye irritation, validation studies are running, but they have not yet provided

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 (Spain; academic) K. Gabrielson (Sweden; animal welfare) B. Garthoff (Germany; industry) K. Pelkonen (Finland; governmental institution) P. Maier (Switzerland; animal welfare + industry) V. Rogiers (Belgium; academic) A. van Iersel (The Netherlands; governmental institution)
2	EU White Paper on chemicals	L. Bansil (UK; industry) K. Gabrielson (Sweden; animal welfare) M. Kayser (Germany; industry) W. Pfaller (Austria; academic) R. Salmi (Finland; animal welfare) H. Spielmann (Germany; governmental institution) M. Weber (Italy, industry)
3	Information & education programmes	J. van der Valk (The Netherlands; animal welfare) A. Smith (Norway, academic)

replacement tests applicable across the full range of chemical substances. For acute lethal toxicity, a validation study on a basal cytotoxicity test has been initiated by the (US) Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and ECVAM (10).

For the testing of biokinetic endpoints, target organ toxicity, systemic toxicity, repeat-dose toxicity, non-genotoxic carcinogenicity, reproductive toxicity, all of strategic importance for the regulatory testing of chemicals according to *Directive 67/548/EEC*, no validated alternative methods are available yet (Table 2).

The EU White Paper on a Strategy for a Future Chemicals Policy

More than 100,000 substances existed on the European market before September 1981, and were taken up on the European Inventory of Existing Commercial Chemical Substances (EINECS). For these, only a limited amount of toxicological data are available, often of rather poor scientific quality.

About 3000 new substances are present on the European List of Notified Chemical Substances (ELINCS), 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 of the resources available today are used for new chemicals.

The EU policy proposes to introduce the REACH system (Registration, Evaluation and Authorisation of Chemicals) with a priority for carcinogenic, mutagenic, reproduction toxic substances (CMRs), persistent organic pollutants (POPs), persistent, bioaccumulative and toxic substances (PBTs) and very persistent and very bioaccumulative substances (vPvBs). Roughly 30,000 existing chemicals produced in amounts higher than 1 tonne/year would be involved.

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

Not available	Available
Photoallergy	Acute oral toxicity
Subacute toxicity	Skin irritation
Chronic toxicity	Phototoxicity
Reproductive toxicity	Ocular irritation
Target organ & systemic toxicity	Skin sensitisation
Biokinetics	Embryotoxicity
Non genotoxic carcinogenicity	

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 of 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.

ECVAM's vision

ECVAM has recently proposed an optimistic strategy plan for the future development and validation of alternative methods (10). However, it is not clear that we should expect that, within the next five to ten years, alternative methods will be available for most, if not all, of the endpoints (10).

Seventh Amendment of 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. for drugs, pesticides, chemicals.

The Sixth Amendment to *Directive 76/768/EEC* (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 use of alternative methods for testing cosmetic products and their ingredients becomes essential.

Sixth Framework Programme (FP6) of the EC for Research, Technological Development and Demonstration Activities

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

However, in the actual Common Position of FP6, no specific key action on alternative methods is being proposed. In addition, almost no mention of alternative methods is made throughout the whole programme text. It is stated that Integrated Projects and Networks of Excellence will contribute to strengthening European competitiveness and to help solve major societal problems by mobilising a critical mass of research and development resources and skills existing in Europe.

Although the time frame of the White Paper and FP6 is nearly the same, no mention has been made 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.

The ECOPA working groups therefore have issued a common position statement on the White Paper (in relation to the FP6). Based on the huge expertise coming from the quadripartite organisation of ECOPA, strong practical and realistic recommendations have been forwarded to the European Commission and the European Parliament.

This statement has been sent to the various EU services concerned, MEPs, politicians, pressure groups, non-governmental organisations, representatives of national platforms, and so on, and is present on the ECOPA website (2). Recently, a conference was organised by the Commission with the different stakeholders, including ECOPA (5), to discuss the state of the art of the Three Rs and to see where problems in the FP6 were present. 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 (section 1.2.1., generally known as priority 8).

Coming initiative of ECOPA

During the EU stakeholders conference in July 2002 (5), it became clear that 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 analyse the difficulties that exist in introducing and implementing alternatives into national, European and supra-national (e.g. the OECD) guidelines and to look for ways to speed up this process. It is in this context that the third ECOPA workshop will be organised (November 8–10, 2002) in Brussels, in collaboration with the OECD.

Conclusions

ECOPA is now a well-organised and structured organisation. It is unique, since it is the only quadripartite organisation at the EU level promoting the Three Rs strategy for the *reduction, refinement and replacement* 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 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 organise scientific and 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 discussions with representatives of the different ECOPA working groups were greatly appreciated.

References

1. Rogiers, V. (2000). The role of national platforms. In *Progress in the Reduction, Refinement and Replacement of Animal Experimentation* (ed. M. Balls, A.-M. van Zeller & M. Halder), pp. 1713–1718. Amsterdam, The Netherlands: Elsevier Science B.V.
2. ECOPA website <http://www.ecopa.tsx.org/>.
3. Anon. (2001). White Paper on a *Strategy for a Future Chemicals Policy*, 32pp. Website <http://www.europa.eu.int/comm/environment/chemicals/whitepaper.htm>.
4. Anon. (2000). Association Internationale a but philanthropique, religieux, 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. & Spielmann, 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. & Zucco, F. (1995). Practical aspects of the validation of toxicity test procedures. The report and recommendations of ECVAM workshop 5. *ATLA* **23**, 129–147.
8. Worth, A. & Balls, M. (2001). The importance of the prediction model in the development and validation of alternative tests. *ATLA* **29**, 135–143.
9. Anon. (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* **p196**, 1–98.
10. Worth, A. & Balls, M. eds. (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. *ATLA* **30**, Suppl. 1, 1–125.
11. Botham, K., Green, E., Holmes, P. & 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. Leicester, UK: IEH. Website <http://www.le.ac.uk/ieh/publications/publications.html>.
12. Anon. (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.
 13. Anon. (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**, 88–103.
 14. Anon. (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.