



Review

# Recent developments in the way forward for alternative methods: Formation of national consensus platforms in Europe

Vera Rogiers\*

*Department of Toxicology, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Laarbeeklaan 103, B-1090 Brussels, Belgium*

Received 11 July 2004; revised 17 December 2004; accepted 21 January 2005

## Abstract

Ecopa, the European Consensus Platform on 3R-Alternatives, is an international not-for-profit organization that wants to stimulate the development of 3R-alternatives, increase awareness among the public, scientists and regulatory bodies, and help their implementation into the different national legislations. This is done by networking and bringing together National Consensus Platforms on 3R-alternatives. Consensus means that all parties concerned are represented, namely, animal welfare, industry, academia, and governmental institutions. Actually, 14 Member State Platforms exist. Fully complying with the criteria, set by ecopa, are the platforms of Austria, Belgium, the Czech Republic, Finland, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom. Under development are the platforms of Denmark, Norway, and Poland. To reach its goals, ecopa uses conventional scientific tools such as workshops and meetings but it also makes scientific–political statements. A recent realization in particular is the involvement of ecopa in several European projects of the Sixth Framework Programme, either as coordinator, research partner, or board member.

© 2005 Elsevier Inc. All rights reserved.

*Keywords:* Alternative methods; In vitro; Ecopa

## Contents

Introduction . . . . .	S408
Discussion . . . . .	S409
Actual status of ecopa . . . . .	S409
The need for platform building on 3R-alternatives . . . . .	S409
Lack of a consistent European vision and strategy on 3R-alternatives . . . . .	S409
Drying up of sources and resources . . . . .	S411
Realizations of ecopa . . . . .	S411
Conclusions . . . . .	S412
References . . . . .	S412

## Introduction

Ecopa stands for European Consensus Platform on 3R-Alternatives (<http://www.ecopa.tsx.org>). It is a quadripartite organization at the EU level promoting the 3Rs strategy for

the replacement, reduction, and refinement of animal experiments in research and regulatory testing (Rogiers, 2000, 2003, 2004). Consensus means that the four parties concerned, namely, animal welfare, industry, academia, and governmental bodies, are represented as well in ecopa as in the individual National Consensus Platforms (NCPs). The latter form the building stones of the umbrella organization. It is believed that progress in 3R-alternatives can best be

\* Fax: +32 2 477 45 82.

*E-mail address:* [vrogiers@fafy.vub.ac.be](mailto:vrogiers@fafy.vub.ac.be).

obtained by collaboration and discussion between the different stakeholders. Of course, initiatives taken by the individual parties are highly appreciated and should continue. Additional progress and results, however, seem to be reachable through strong networking and teaming up of all stakeholders in Europe.

## Discussion

### *Actual status of ecopa*

The statutes of ecopa have been officially published (Anonymous, 2004) and are present on the ecopa website (<http://www.ecopa.tsx.org>). Also, the set of criteria with which national platforms (NP) should comply in order to be recognized as NCPs is provided. Ecopa started in 1999 counting 3 members (Rogiers, 2000). Today, 14 members are present, of which 11 are full members and 3 associate ones. The former comply with all criteria set by ecopa, whereas the latter are in the process of building a platform and becoming a legal entity within their own country. In Table 1, the

different national consensus platforms on 3R-alternatives are shown.

According to the rules of an international not-for-profit organization, ecopa's Board and Executive Board members, and three 3R-experts have been elected by the General Assembly. The actual compositions are given in Table 2. The association functions through four working groups. Their fields of competence and interest are research, chemical and environmental EU policy, and education and ethics, respectively. These fields of interest can be changed according to the most urgent needs in the field of 3R-alternatives.

### *The need for platform building on 3R-alternatives*

Basically, there are several important reasons why strengthening of forces and bundling of efforts by all stakeholders seem to be crucial. These are in particular concerned with (i) lack of a consistent European vision and strategy on 3R-alternatives, and (ii) drying up of sources and resources.

### *Lack of a consistent European vision and strategy on 3R-alternatives*

During the last 30 years, efforts have been made by all stakeholders to develop 3R-alternatives, and to validate and practically apply these. However, during this process, no clear distinction was made between the development and use of alternatives in either research or regulatory testing. As far as the availability of alternatives for research purposes is concerned, the actual situation is good and a lot of alternative methodologies (e.g., cell and tissue culture) and new technologies (e.g., “-omics”) exist to elucidate mechanisms of action or toxicity, for example, in preclinical drug development. The situation, however, becomes quite different when alternative methods are considered for regulatory purposes, namely, to be used as replacement methods for the *in vivo* methods used in regulatory testing of safety of chemicals, drugs, agrochemicals, food, and cosmetics. It is not always realized by all stakeholders that, for regulatory testing, the lack of alternative methods, developed for that particular purpose, is rather dramatic. The actual lack of 3R-alternative methods for regulatory testing purposes has been clearly recognized by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) (CSTEE, 2004), by the European Centre for the Validation of Alternative Methods (ECVAM) (ECVAM, 2004), and by the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) (SCCNFP, 2004).

Before chemicals, drugs, agrochemicals, food additives, and cosmetics come on the EU market, their safety for man and his environment must be guaranteed. This is done by keeping a so-called toxicological dossier. Without going into details, such a dossier contains in particular *in vivo* results of experiments carried out with laboratory animals.

Table 1

Existing consensus platforms on 3R-alternatives in Europe: full and associate members of ecopa

National Consensus Platform (NCP)	
<i>Full ecopa members</i>	
Country, NCP name	Responsible
Austria, Zentrum für Ersatz- und Ergänzungs-methoden zu Tierversuchen (ZET)	Walter Pfaller
Belgium, Belgian Platform for Alternative Methods to Animal Testing (BPAM)	Jean-Paul Beaufays
Czech Republic, Consensus Platform of the Czech Republic for Alternatives to Animal Testing (CZECOPA)	Dagmar Jírová
Finland, Finnish Consensus Platform for Alternatives (FINCOPA)	Hanna Tähti
Germany, Stiftung zur Förderung der Erforschung von Ersatz- und Ergänzungsmethoden zur Einschränkung der Tierversuchen (set)	Bernward Garthoff
Italy, Italian Platform on Alternative Methods (IPAM)	Annalaura Stamatii
The Netherlands, Alternatives to Animal Experiments Platform	Iris Arendzen
Switzerland, 3R Research Foundation	Peter Maier
Spain, Red Española de Métodos Alternativos: Spanish Network on Alternative Methods (REMA)	José Castell
Sweden, Swedish Platform for Alternatives	Karin Gabrielson
United Kingdom, The Boyd Group	Kenneth M. Boyd and Jane Smith
<i>Associate ecopa members</i>	
Country:	Coordinator:
Denmark	Ove Svendsen
Norway	Adrian Smith
Poland	Maciej Stepniak

Table 2  
Actual composition of ecopa Board

Executive	Board Persons involved	Function
Daily follow-up,	Vera Rogiers (B, Ac)	Chairperson
elected by	José Castell (E, Ac)	Vice-chairperson
General	Bernward Garthoff (D, I)	Treasurer
Assembly		
Board		
Elected NCP	Peter Maier (CH, AnW/I)	
members by	Karin Gabrielson (S, AnW)	
General	Walter Pfaller (A, Ac)	
Assembly	Arthur van Iersel (NL, G)	
3R-experts		
Elected by	Coenraad M. Hendriksen	
General	(NL, Ac)	
Assembly	Horst Spielmann (D, G)	
	Flavia Zucco (I, AnW)	

Ac: Academic; I: Industry; AnW: Animal Welfare; G: Governmental.

However, (Q)SAR [(Quantitative) Structure Activity Relationship] data, physicochemical data, clinical data, and the outcome of epidemiological studies also are present. For the last few years, there is also a tendency to include in vitro data, obtained through validated alternative methods [taken up in annex V of the Dangerous Substances legislation or in the Organization for Economic Cooperation and Development (OECD) Guidelines]. From data given in the 3rd Commission Report on the Statistics on the Number of Animals Used for Experimental and Other Scientific Purposes in the EU, it can be seen that most animals (61%) for toxicological or other safety evaluations are situated in medicine, of which one third is destined for quality control of biologicals (Fig. 1). Environmental contaminants take 15%, industry 12%, and agriculture 10%.

Cosmetics consume only 1% of all animals used in toxicological studies and/or safety evaluations. When animal consumption is considered per type of regulatory toxicological test, the highest animal use occurs in acute

systemic toxicity testing (35%) (Fig. 2), followed by chronic toxicity tests (17%), reproductive toxicity tests (13%), and repeated dose testing (10%). The development of alternative methods is thus of high priority if one wants to reduce the number of animals that are nowadays considered to be necessary for safety evaluation of human health and environment. A number of 3R-alternative methods already exist (ECVAM, 2004), but still a lot of gaps need to be identified. Prioritization, coordination, and the maintenance of realistic time frames become key issues with which the Commission should correctly deal with (SCCNFP, 2004).

In Europe, setting of priorities is done vertically, meaning that specific provisions are built into the specific legislation for a particular group of products. A typical example is the cosmetic legislation. Where the Sixth Amendment (Anonymous, 1993) already envisaged the replacement of animal tests by in vitro alternatives from the moment they were available and generated the same level of knowledge, the more recently published “Seventh” Amendment (Anonymous, 2003) now imposes strict deadlines for the abolition of animal testing, not only for finished products, but also for their ingredients. More specifically, it imposes a prohibition of in vivo animal studies on cosmetic ingredients from March 11, 2009 onwards, with the exception of repeated dose toxicity, toxicokinetics, and reproduction toxicity tests, which will be prohibited from March 11, 2013 onwards. This testing ban is enforced by a marketing ban imposed on any cosmetic product and/or cosmetic ingredient that has been subject to testing through an animal method for which an alternative has been adopted (Anonymous, 2003). This means that even reduction and refinement tests available today such as the murine local lymph node assay (LLNA) for skin sensitization OECD 429 and the acute toxicity methods (up-and-down procedure OECD 425, fixed dose procedure OECD 420, acute toxicity class procedure OECD 423) can no longer be applied for cosmetics after March 2009. Clearly, a horizontal approach is needed, linking all existing EU legislations to each other. Indeed, the use in all

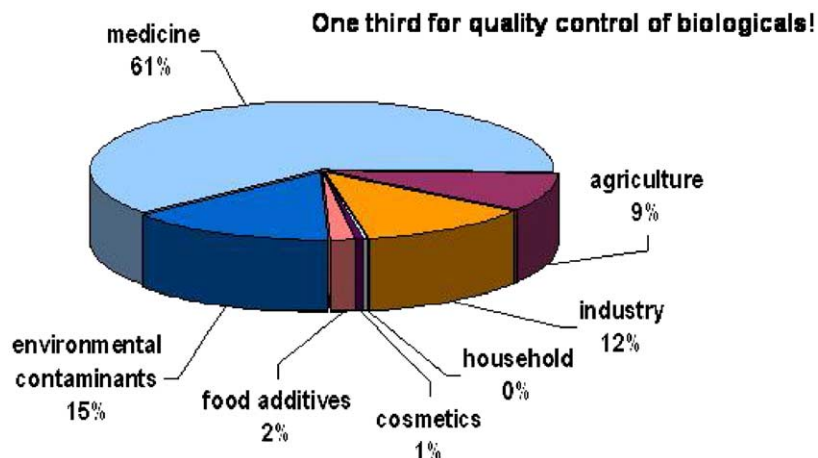


Fig. 1. Animals used in toxicological or other safety evaluations. (Reference: 3rd Commission Report on the Statistics on the Number of Animals used for Experimental or Other Scientific Purposes in the EU).

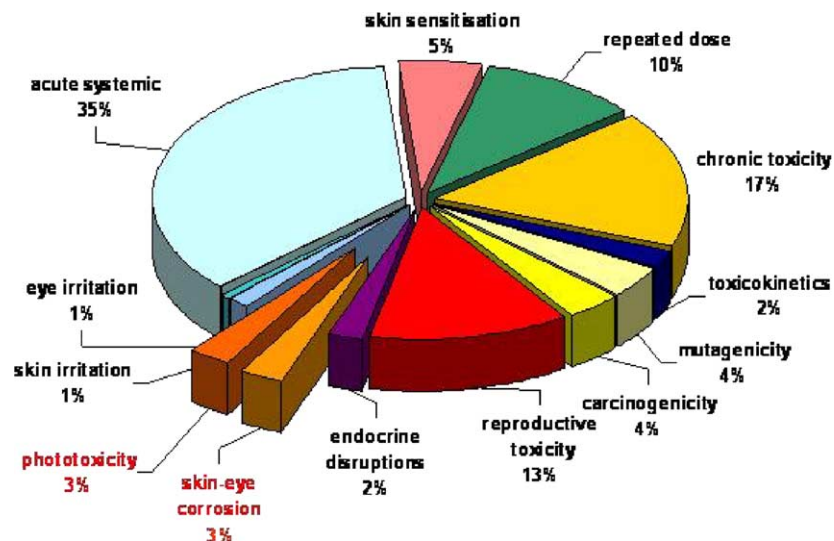


Fig. 2. Animals used in toxicological evaluations per year. (Reference: 3rd Commission Report on the Statistics on the Number of Animals used for Experimental or Other Scientific Purposes in the EU).

potential fields of application of a validated alternative method, from the moment it becomes available, would lead to a more efficient reduction in animal use than is the case today with the vertical approach.

#### *Drying up of sources and resources*

The EU chemical policy for the near future is REACH (Registration, Evaluation and Authorization of Chemicals) with a priority for carcinogenic, mutagenic, reproductive toxic substances (CMRs), persistent organic pollutants (POPs), persistent bioaccumulative and toxic substances (PBTs), and very persistent and very bioaccumulative substances (vPvBs) (Anonymous, 2001; Lind, 2004). In the actual proposal, it is indicated that a scientific objective for the EU is the development and validation of alternative methods and that such methods must be considered as they become available. However, the problem is that the alternative tests needed for regulatory purposes of chemicals are not currently available. As indicated in the CSTEE (2004), ECVAM (2004), and SCCNFP (2004) reports mentioned earlier, the gaps between *in vitro* and *in vivo* methods have not yet been fully identified, and for those that have been identified, only a limited number of 3R-alternatives exist. To mention only a few: subchronic and chronic toxicity, non-genotoxic carcinogenicity, reproductive toxicity, target organ toxicity, photoallergy, and others. Since for these *in vivo* tests no alternatives are available today, validation is not possible. For some of these fields, research projects have been initiated with the support of the Sixth Framework Research Programme of the EU (e.g., ReProTect, AcuteTox, Predictomics); however, as these projects only start now, the first results can only be expected within 5 years. Validation is a time-consuming activity which can only start after proper development of a relevant method and its prevalidation. From the past, it is known that

it may take up to 8 years to have a method ready and implemented into the legislation. Having in mind that for certain endpoints no acceptable proposals for development exist, the time frames set by the Parliament and the Commission seem to be highly unrealistic.

A literature search over the past 6 years (1998–2003) was carried out using standard databases including Chemical Abstracts, Medline, Embase, Biosis, Scisearch, Derwent Drug Pat., SCRIP Ring doc-ZEBET, ICCVAM (The Inter-agency Coordinating Committee on the Validation of Alternative Methods), and Monographs (Garthoff, 2003). It appeared that, of the many articles published on the topic of 3R-alternatives, most are reviews and only a limited number are original research articles: 22 new approaches were counted over a time frame of 6 years. It seems that new ideas and good research proposals are missing. This became also clear from the low number of research proposals on 3R-alternatives that was sent in during the first two calls of the Sixth Framework Research Programme of the EU. One of the reasons for this low interest could be that the EU procedure is very heavy and time consuming, scaring off scientists from both industry and the academic world. However, the Commission could also perceive it as a lack of innovative ideas which could have consequences for 3R-alternatives as a research priority in the Seventh EU Research Programme. Consequently, action of all stakeholders is needed.

#### *Realizations of ecopa*

Realizations of ecopa are situated in different fields and usually related to activities of the working groups.

- (i) In the scientific–political field: 4 annual workshops (5th on 26–28 November, 2004) on politically sensitive scientific issues, such as REACH, have been

realized in collaboration with important stakeholders such as ECVAM, OECD, DG Research, DG (Directorate General) Enterprise, and others. On the occasion of the Internet Consultation organized by the Commission (on REACH), inviting comments before finalizing the REACH proposal and sending it to the European Parliament and Council for consideration, ecopa published its position on its website. A sign-in procedure was initiated, and as a consequence of high support from the different stakeholders, a strong document could be forwarded to the Commission.

- (ii) In the field of networking and spreading of information on 3R-alternatives: the ecopa website was expanded and updated giving links with the different NCPs. Also, the creation of a newsletter, containing information on ongoing EU projects in the 6th Framework Programme and important “-omics” projects, has been realized. It is called “ecopa messenger”. Efforts to build platforms in already joined EU countries and in the new EU countries are going on and consensus platforms in Poland, Norway, and Denmark are expected to be fully functional during 2005. A start has been made also to build a platform in Hungary and Slovenia.
- (iii) For education: the ecopa website provides up-to-date information on courses on 3R-alternatives in Europe and in particular on those initiated by the NCPs. Several links with other websites, active in the field of education, are provided.
- (iv) For research: most realizations of ecopa are in science. Several projects on 3R-alternatives proposals were forwarded to DG Research as a response to the different calls of the 6th Framework Programme, and most of these were successful. As such, ecopa’s chairperson is coordinator of the CONAM project on Consensus Networking on Alternative Methods. It is a 3-year SSA (Specific Support Action) project with basically the same aims as ecopa and with emphasis on networking and NCP building in the new EU countries. Another EU-supported ecopa project is PREDICTOMICS, which is the acronym for “Short-Term Models for Long-Term Toxicity”. Coordination of this STREP (Specific Targeted Research Project) is taken care of by ecopa’s vice-chairperson. Several NCP members from industry and academia are involved as research partners. The project runs for 3 years. Projects for which ecopa is present in the Supervising and Advisory Board, respectively, are ReProTect and AcuteTox. Both are large IP (Integrated Projects), running for 5 years and concerned with new testing strategies in the field of reproductive toxicity and acute oral toxicity, respectively. A new project of ecopa for the near future is “eSI” (ecopa Science Initiative), which aims at bringing top scientists and young promising researchers together. The concept is based on “thinking about and for

alternatives” and wants to stimulate the incorporation of new ideas from other research fields into 3R-research. Goals are to improve the scientific level of research on 3R-alternatives and increase recognition of science on 3R-alternatives.

## Conclusions

Ecopa is now a good functioning and well-structured organization counting 14 NCPs among its members. It has shown, within the relative short time of its existence, that it is an active organization based on sound science. Several scientific initiatives are supported by the European Sixth Framework Programme for Research and provide a solid basis for further development. For the near future, the eSI project is important since it aims at involving young scientists into 3R-research. Indeed, ecopa believes that the field of 3R-alternatives needs rejuvenation and new ideas. The level of science and the too small basis of 3R-research can be improved by attracting top scientists from other disciplines that might be relevant to alternative method development, and bringing them in contact with young promising scientists. Focus will also be on identifying the “hidden” cases for the follow-up development, in academia, SMEs (small and medium enterprises), biotech start-up companies, etc. Country initiatives, also in the new or candidate EU states can contribute substantially. Efforts by all stakeholders are needed to improve the level of science and to make a new breakthrough possible.

## References

- Anonymous, 1993. 93/35/EEC-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 L 151, 32 (23/06/1993).
- Anonymous, 2001. White paper on a strategy for a future chemicals policy [COM (2001) 88 final] Website: <http://europe.eu.int/comm/environment/chemicals/whitepaper.htm> (accessed 8/1/2001).
- Anonymous, 2003. 2003/15/EC-Directive 2003/15/EC of the European Parliament and of the Council of 27 February 2003 amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products. Official Journal L 66 (11/03/2003), p. 26.
- Anonymous, 2004. Bijlagen bij het Belgisch Staatsblad, Annexes du Moniteur belge, 21-04-2004, number 04061510.
- CSTEE—Opinion of the Scientific Committee on Toxicity, Ecotoxicity and the Environment on the BUAV-ECEAE report on “The way forward—Action to end animal toxicity testing” Doc. C7/VR/csteeop/anat/08014 D(04) European Commission, 2004. (ecopa website:). <http://www.ecopa.tsx.org>.
- ECVAM-Report for establishing the timetable for phasing our animal testing for the purpose of the cosmetics directive, 30 April 2004
- Garthoff, B., 2003. Alternative Methods Development. Pipeline: Sufficient Projects in Face of EU Chemical White Paper and Cosmetic Legislation? Report on 4th European Workshop of National Platforms on Alternative Methods, 28–30 November, 2003, Brussels. (<http://ecopa.vub.ac.be>).

- Lind, G., 2004. In: Schörling, I. (Ed.), REACH—What Happened and Why? The Only Planet Guide to the Secrets of Chemicals Policy in the EU. European Parliament, Brussels, pp. 1–145.
- Rogiers, V., 2000. In: Balls, M., van Zeller, A.M., Halder, A.M. (Eds.), The role of National Platforms in Progress in the Reduction, Refinement and Replacement of Animal Experimentation. Elsevier Science B.V., Amsterdam, pp. 1713–1718.
- Rogiers, V., 2003. Ecopa: actual status and plans. *Toxicol. in Vitro* 17, 779–784.
- Rogiers, V., 2004. The European consensus platform on three Rs alternatives. *ATLA* 32 (suppl. 1), 349–353.
- SCCNFP opinion concerning “Report for establishing the timetable for phasing out animal testing for the purpose of the cosmetics directive (issued by ECVAM 30/04/2004), 1 July 2004, adopted by written procedure.