White Paper on the Future Chemical Policy in the European Union – Implications for Animal Welfare

Ursula G. Sauer
Akademie für Tierschutz, D-Neubiberg

Summary
In February 2001, the European Commission adopted a White Paper on a Future Chemicals Policy. Its main goals are better to protect humans and the environment from unknown risks through chemicals. The "promotion of non-animal testing" is one of the key elements of the proposed strategy. For low production volume chemicals, only data from in vitro tests are to be requested. The data requirements for higher production volume chemicals shall be designed flexibly so that only data relevant for the respective chemical are collected. From the point of view of animal welfare concrete risk management strategies should be defined before test batteries are put together. The test catalogues currently listed in the Classification Directive 67/548/EEC are to be replaced by tiered testing strategies, and concrete waiving strategies are to be designed so that the requested tailor-made testing can actually be realized. Another essential prerequisite for the promotion of non-animal testing is that the funding of alternative method research is formulated as a key action with a concrete budget in the Sixth Research Framework Program of the European Union.

Zusammenfassung: Das Weißbuch für eine zukünftige EU-Chemikalienpolitik – Tierschutzrelevante Aspekte
Im Februar 2001 hat die Europäische Kommission ein Weißbuch für eine zukünftige Chemikalienpolitik vorgelegt. Ziel ist es, den Menschen und die Umwelt besser als bisher vor unbekannten Gefahren durch Chemikalien zu schützen. Im Weißbuch wird „Förderung von Prüfungen ohne Versuchstiere" als eines der Schlüsselelemente der neuen Chemikalienpolitik genannt. Um dies zu verwirklichen, sollen für niedrigvolumige Stoffe nur Daten aus in vitro Verfahren vorgeschrieben werden. Die Datenanforderungen für höhervolumige Stoffe sollen flexibel gestaltet werden, so dass nur die für die Bewertung des jeweiligen Stoffes notwendigen Tests durchgeführt werden. Aus der Sicht des Tierschutzes ist weiterhin zu fordern, dass konkrete Risikomanagementstrategien festgelegt werden, bevor Testbatterien ausgestaltet werden. Die Testbatterien, die derzeit in der Klassifizierungsrichtlinie 67/548/EEC aufgeführt werden, sind durch stufenweise hierarchisierte Testreihen zu ersetzen. Die Forderung nach zugeschnittenen Testbatterien muss so ausgestaltet werden, dass sie in der Praxis greifen kann. Wesentlich ist auch, dass die im Weißbuch formulierte Forderung der verstärkten Förderung tierversuchsfreier Verfahren im 6. Forschungsrahmenprogramm der EU konkret umgesetzt wird.

Keywords: chemicals, legislation, safety testing, risk management, in vitro toxicity, test strategies

1 Background

The great majority of chemicals currently in use are so-called existing chemicals that were put on the market before 1981, when there was no legislation in force regulating the marketing or use of chemicals. 100.106 chemicals are listed in the European Inventory of Existing Commercial Chemical Substances (EINECS) and are regulated by Council Regulation (EEC) 793/93 on the evaluation and control of risks of existing substances (OJ L 84, 5.4.1993, p.1). It is recognised that for the vast majority of the existing chemicals the effects on humans or the environment are unknown (Danish Board of Technology, 1996).

In contrast, only approximately 2.400 chemicals have been put on the market after 1981 and are thus listed as new chemicals in the European List of Notified Chemical Substances (ELINCS). The major legal instruments currently in force in the European Union in regard to the marketing and use of new chemical substances and preparations are Council Directive 67/548/EEC relating to the classification, packaging and labeling of dangerous substances, as amended (OJ 196, 16.8.1967, p. 1), Directive 88/379/EEC relating to the classification, packaging and labeling of dangerous preparations (OJ L 187, 16.7.1988, p. 14) and Directive 76/769/EEC relating to restrictions on the marketing and use of certain dangerous substances and preparations (OJ L 262, 27.9.1976, p. 201).

On November 18th, 1998, the Commission adopted a report on the evaluation of the EU legislation on industrial chemicals (Commission of the European Communities, 1998). It was acknowledged that there was a general lack of knowledge about the properties and the uses of existing substances. The risk assessment process was recognised to be slow and resource-intensive and not to allow the sys-

tem to work efficiently and effectively. In consequence, in June 1999, the Council of Environmental Ministers assigned the General Directorates Environment and Enterprise (DG ENV and ENTR) of the European Commission with the joint task to submit a policy document outlining a new chemicals strategy by the end of the year 2000. After a small delay, this White Paper for a future Chemicals Policy was adopted on February 13th, 2001 (Commission of the European Communities, 2001a).

2 Future EU chemicals policy – political developments relevant for animal welfare

In the White Paper, seven key elements of the strategy for a new Chemicals Policy are defined, such as the protection of human health and the environment and different economical factors. Number six of the seven key elements is the "*promotion of non-animal testing*". This key element is subdivided into three objectives:

"Maximising use of non-animal test methods: Testing requirements will be met as far as practicable through use of existing non-animal test methods.

Encouraging development of new non-animal test methods: Development of new non-animal test methods will be encouraged.

Minimising test programs: Measures to increase testing thresholds and more flexible test regimes will limit the need for testing."

Chapter 3.2. of the White Paper further specifies how laboratory animals are to be protected in a revised chemicals policy: *"The following elements of the new system have been developed with a view to keep animal testing to a minimum:*

▶ *Existing information on the toxicity and ecotoxicity of substances, including epidemiological studies, will be taken into account,*

▶ *The general testing requirements will be modified to incorporate exposure-driven testing where appropriate,*

▶ *Tailor-made testing programmes for substances will be developed under the control of authorities for Level 1 and 2 testing,*

▶ *The development of further alternative testing methods using fewer or no animals will be fostered,*

▶ *Existing substances will be grouped to minimize testing, where appropriate."*

It is planned to replace the current notification system for new chemicals by the REACH system, which calls for the **R**egistration, **E**valuation or **A**uthorization of **Ch**emicals, depending on their production volume and level of concern. It shall be applied both to new and existing chemicals. Among other issues, the production volume of the chemical will determine the amount of data required for the marketing of a specific substance. For substances produced or imported in quantities between 1–10 tonnes "*data on the physicochemical, toxicological and ecotoxicological properties of the substance*" are to be requested and it is stated: "*Testing should generally be limited to in vitro methods.*"

When turning the strategy depicted in the White Paper into a new EU legislation on chemicals, the European Commission has to take into account the comments on the White Paper made by the Environment and Internal Market Council and by the European Parliament. The Council of Environmental Ministers discussed the White Paper during their 2355th session on June 7th, 2001 in Luxembourg. In conclusion No. 23 published as an outcome of this discussion (Council, Environment, 2001), the Council underlines that: "*...animal testing should be limited to the level necessary to deliver the objectives of the strategy, including a high level of protection for human health and the environment. Industry should make all existing data available to avoid duplication of testing. Mechanisms are needed to ensure that unnecessary testing requirements are avoided. Adequate resources must be provided for research, development and validation of globally accepted test guidelines for alternative in vitro test methods, so that work can be accelerated at all levels. Activities under the new Framework Programme for Research should consider these requirements among its priorities. In addition to promoting this issue in ECVAM, the Community should play a more active role in the OECD, to encourage wider adoption of validated, alternative, non-animal testing methods.*"

In addition, in conclusion No. 40, the Council invites the Commission, "*to study how to develop screening procedures to effectively identify chemicals with potentially harmful properties or uses of concern for the purposes of prioritising substances for which further information is urgently needed and those requiring accelerated risk management*" and (Council Conclusion No. 42) to "*...study further the data requirements for substances produced in volumes below 10 tonnes in order to ensure that the information provided will be sufficient for classification and labeling and to assess the need for risk reduction measures. The data sets must also provide appropriate information for handling cases of unintentional releases and to enable the protection of the health and safety of workers whilst ensuring a minimum of animal testing.*"

The European Parliament, as of the beginning of November 2001, has not yet put forward a final opinion on the White Paper. However, a report on the White Paper has been prepared by MEP Inger Schörling (European Parliament, 2001), which has been voted on in the Committee on the Environment, Public Health and Consumer Policy of the European Parliament on October 16, 2001. In this amended but not finalised report, Recital T states: "*...animal tests must be replaced with more humane alternatives, and coordinated action is needed to bring new non-animal tests into use.*" Paragraph 13 of the draft report states that the European Parliament "*calls on the Commission to ensure that animal testing is reduced to the absolute minimum, firstly by ensuring that all existing data is made available and considered, and secondly by implementing, as far as possible, a stepwise non-animal testing strategy, that makes full use of computer models that predict hazards based on chemical structure (QSAR), as well as of physicochemical tests for persistency and bioaccumulation, and cascades of in vitro tests, also with a view to reducing testing time and costs.*"

3 Ways to implement the promotion of non-animal testing in a new chemicals policy

From the point of view of animal welfare the deficiencies in the current chemicals policy are also an evidence for the shortcomings of animal testing strategies, be-

ing that the testing strategies are either too cumbersome to be pursued on a large scale or that the animal tests performed are not relevant enough to lead to appropriate decisions. Furthermore the shortcomings of the current system are caused by deficiencies in strategies on how to manage risks caused by dangerous substances.

It is the aim of the White Paper to overcome these problems and to ensure that human health and environmental integrity are not put at risk by man-made chemicals and at the same time to avoid the use of animal tests. The Environment Council has confirmed these goals, and it can be foreseen that the European Parliament will also confirm them. However, these goals can only be reached if the key elements of the new strategy to "maximise" the use of alternatives, to "minimise" the use of animal tests, and to achieve "flexibility" in testing strategies are further elaborated and specified.

3.1 Risk management strategies

The appropriate starting point for developing a new chemicals policy is the development of risk management strategies. Before risks are determined through any kind of evaluation, sound risk management strategies have to be agreed upon. It is imperative that the bodies involved decide on actions to be taken when specific chemicals are found to have certain hazardous properties. And these decisions have to be made before chemicals are actually tested and evaluated. In the next step, the need for particular types of information has to be identified and prioritised and the appropriate method of obtaining the necessary information has to be determined. For example, if the responsible bodies agree that certain products would be considered unacceptable when found to be bioaccumulative or persistent, the determination of these characteristics would render further testing such as toxicity testing unnecessary.

3.2 Safety testing strategies

Non-animal testing strategies should not apply to low production volume chemicals only, as depicted in the White Paper, but to all levels of production volume. In order to avoid animal tests and at the same time to ensure maximum safety to humans and the environment, the following stepwise testing strategy is to be recommended in line with the strategy demanded in the draft report adopted by the Environmental Committee of the European Parliament:

In the first step, all existing information on the respective substance and on substances with similar structure is to be collected, making use of data available in the industry, with the authorities, and also at scientific and medical centers. In the next step, hazard prediction shall be made based on the structure of the chemical, for example by means of QSAR models. The following step covers the evaluation of physico-chemical properties and the performance of persistency and bioaccumulation tests. Next, a battery of basic *in vitro* tests is to be applied covering endpoints such as basal cytotoxicity, *in vitro* mutagenicity, skin penetration and corrosivity, *in vitro* metabolism and *in vitro* ecotoxicity. Taking into account the results of this initial battery of *in vitro* testing, in the following step a battery of specific *in vitro* tests should be applied with the performance of cell transformation tests and evaluations of the effects on specific cell types such as embryonic stem cells, hepatocytes or neurons.

After each step it should be evaluated if a classification of the respective substance is already possible. For the safety of humans and the environment, substances that provide reason for concern in non-animal tests should be classified accordingly without further testing. The question of whether an animal test should be performed for the classification of a chemical should only be put forward after all possibilities to collect the necessary data without animals have been taken into account. When deciding whether to perform a specific animal test, advice from experts in the field of alternative methods should be sought.

3.3 Waiving mechanisms

A clear strategy on when to omit which tests should be developed tailoring testing according to the results of the evaluation of existing data, physico-chemical properties, the use and the exposure to the substance. This strategy should be implemented in concrete official guidelines and must allow every possible opportunity to avoid animal and non-animal testing and to classify a given chemical making use of the minimum information necessary for that purpose.

3.4 Funding of alternative test development and validation

It is scientifically feasible to determine the relevant toxicological and ecotoxicological endpoints without animals. However for many endpoints officially accepted non-animal test methods are not yet available. In order to overcome this deficit, the status of alternative methods must be identified for each relevant endpoint, distinguishing between endpoints, for which accepted alternatives exist or, respectively, validated alternatives, alternatives in the process of prevalidation, alternatives in the process of development, or only scientific proposals on how a specific endpoint could be evaluated without animals.

In the White Paper concrete deadlines for the registration of chemicals have been set down. Therefore immediate action to close the respective knowledge gaps is indispensable, if significant progress is to be made in developing, validating and accepting non-animal test methods in time to have an impact on the testing to be done in order to meet these deadlines, and a substantial amount of funding is required. Initially this work should focus on those endpoints that will be requested at base set level and on those tests with the greatest potential to save animals in regard to the registration of existing chemicals, for example *in vitro* sensitisation tests or *in vitro* skin and eye irritation tests.

Thus, research in alternative methods for the testing of chemicals should become a priority key action in the sixth Framework Programme for Research currently under discussion on the level of the European Union. The Environment Council has explicitly formulated this same request, and reference is made to it in the draft report of the European Parliament. In addition, national funding programmes in the EU member states should supplement EU funding.

So far, this demand has only partly been taken up. In October 2001, the European Commission (Commission of the European Communities, 2001b) has proposed a series of initial research priorities with the aim of "*providing health, security and opportunity to the people of Europe*". It is stated that research in this area will focus

on (amongst other issues) the "*development of improved methods for risk assessment, including non-animal test methods for chemical substances*". Whereas this statement is to be welcomed, a specified and adequate amount of the research budget remains to be designated to this area of research in order to ensure that the goal will be met.

It is to be noted that the task of determining the current status of alternative methods for all relevant toxicity test endpoints has been taken up by ECVAM, the European Centre for the Validation of Alternative Methods of the Joint Research Centre of the European Commission. A document covering the outcome of their work is currently under preparation. This document should be taken into account when designing testing strategies for the new chemicals policy and also when determining areas of priority for funding in alternative method research and for the funding of alternative method validation studies.

When validating alternative methods and when deciding on their acceptability, the hurdles set should not be higher than those set for the acceptance of animal tests. In order to speed up the acceptance of new alternative methods, the request of the Environment Council, that the European Commission should play a more active role on the level of the OECD should be taken into regard. In addition classifications schemes for the relevant endpoints applicable to the respective alternative test methods have to be designed and agreed upon.

4 Conclusions

In the White Paper for a future chemicals policy in the European Union a high goal has been set, that is to design a new policy that will improve the safety for humans and the environment and at the same time to minimise animal testing. It is possible to reach this goal if all responsible bodies and organisations involved cooperate and strive to reach the objectives laid down in the White Paper. However, a lot remains to be done, and substantial financial support is needed.

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Correspondence address
Dr. med. vet. Ursula G. Sauer
Akademie für Tierschutz
Spechtstrasse 1
D-85579 Neubiberg
Tel.: +49 89 600 201 0
Fax.: +49 89 600 291 15
ursula.sauer@tierschutzakademie.de