

# The New EU Chemicals Policy: Challenges and Chances for Animal-free Test Methods

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**Summary** — As a first step toward preparing new chemicals legislation, in February 2001, the European Commission adopted a White Paper on a *Strategy for a Future Chemicals Policy*. Its main goals are to better 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 will be designed flexibly, so that only data relevant for the respective chemical are collected. From the point of view of animal welfare risk management, strategies should be defined before test batteries are put together. The test catalogues currently listed in the Dangerous Substances Directive, *Council Directive 67/548/EEC*, are to be replaced by flexible, tiered-testing strategies, and concrete waiving strategies are to be designed. The avoidance of duplicate testing should become mandatory. In order to fill prevailing knowledge gaps, the funding of alternative method research should be given priority by the EU Commission, and thus should receive a concrete budget. It should have been formulated as a key action in the European Sixth Research Framework Programme.

**Key words:** *chemicals, data sharing, regulatory toxicity, research funding, testing strategies.*

## Introduction

The great majority of chemicals currently in use are the so-called existing chemicals that were put on the European market before 1981, when there was no legislation in force regulating the marketing or use of chemicals. *The European Inventory of Existing Commercial Chemical Substances* (EINECS) lists 100,106 chemicals, and these chemicals have since been covered by *Council Regulation 793/93/EEC* on the evaluation and control of risks of existing substances (1). It is recognised that for the vast majority of these existing chemicals, the effects on humans or the environment are unknown (2).

In contrast, only approximately 2400 chemicals have been put on the market since 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 (EU) with regard to the marketing and use of new chemical substances and preparations are *Council Directive 67/548/EEC*, relating to the classification, packaging and labelling of dangerous substances (3), *Council Directive 88/379/EEC*, relating to the classification, packaging and labelling of dangerous preparations (4) and *Council Directive 76/769/EEC*, relating to restrictions on the marketing and use of certain dangerous substances and preparations (5).

On 18 November, 1998, the Commission adopted a report on the evaluation of the EU legislation on

industrial chemicals (6). 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 system 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 DG 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 on a *Strategy for a Future Chemicals Policy* was adopted on 13 February 2001 (7).

The setting up of new legal instruments for the revised EU Chemicals Policy is a co-decision procedure. The European Commission will take into account the European Parliament resolution on the Commission White Paper (8) and the relevant Council Conclusions of the Environment and Internal Market Council when drafting the new pieces of legislation. The Council of Environmental Ministers formed their opinion on the White Paper during their 2355th session, on 7 June 2001 in Luxembourg (9).

## Animal Welfare Issues in the White Paper

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:

1. *Maximizing use of non-animal test methods: testing requirements will be met as far as practicable through use of existing non-animal test methods.*
2. *Encouraging development of new non-animal test methods: development of new non-animal test methods will be encouraged.*
3. *Minimizing 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 Registration, Evaluation and Authorisation of Chemicals, 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 physico-chemical, toxicological and ecotoxicological properties of the substance” are to be requested and it is stated: “testing should generally be limited to *in vitro* methods”.

The Environmental Council (9) 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 prioritizing 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.*

In the European Parliament Resolution on the Commission White Paper (8), 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 33:

*... calls on the Commission to ensure that animal testing is reduced to the absolute minimum, firstly by ensuring that all relevant data is made available and considered, secondly by basing further tailor-made tests on exposure and use and thirdly by implementing, as far as possible, a step-wise non-animal testing strategy, that makes full use of computer models that predict hazards based on chemical structure (QSAR [quantitative structure–activity relationship]), as well as of physico-chemical tests for persistency and bioaccumulation, and cascades of *in vitro* tests which are recognized by the authorities, also with a view to reducing testing time and costs.*

## Discussion

### 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 evidence of the shortcomings of animal testing strategies, as 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 human-made chemicals, while also avoiding the use of animal tests. 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.

### 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. 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.

### 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 step-wise testing strategy is to be recommended in line with the strategy demanded in the European Parliament Resolution (8).

In the first step, all existing information on the respective substance and on substances with simi-

lar 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 whether 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.

In the White Paper, it is stated that the data requirements should be tailored to a specific substance to ensure that only those data are collected that are actually necessary for the respective evaluation. However, while this request goes undisputed, controversial opinions have been put forward on how best to implement it.

Many representatives from national authorities call for a fixed test catalogue to be laid down for each production volume category. If a company submitting a registration dossier believes that it does not have to perform one of the tests of the catalogue, it must justify this decision, and this justification will be subject to acceptance by the authorities. The company must either prove that the data requested are already provided through other data, or that it is not necessary to provide the respective data at all, either for scientific or technical reasons, or because the expected exposure scenario renders the data irrelevant. It is argued that this would be the only way to ensure that incomplete data sets are no longer submitted for registration.

The animal welfare movement, on the other hand, is in favour of implementing a more flexible concept in the new chemicals legislation. They are in favour of a flexible step-wise tiered testing strategy, in which the data collected would be evaluated after each step of the testing, and decisions on remaining data requirements would be made upon the results of the steps previously performed (10).

Those favouring the more flexible strategy contend that it puts more emphasis on the specific data requirements tailored to a specific substance. Thus, it encourages the avoidance of unnecessary tests by ensuring that the data collected are evaluated scientifically already during the data gathering process. Taking into account the fact that the White Paper aims at placing the responsibility for the safety of a chemical on the industry, it would seem appropriate to assign industrial toxicologists with the task to decide on the data requirements necessary for a specific registration. In order to improve the transparency of the decision strategies, the company should be obliged to provide justification of its decisions upon registration. However, care should be taken that such a request for justification does not become an unsurpassable hurdle that would prevent the waiving of tests.

There are two prerequisites for the success of flexible testing strategies. First, it is of paramount importance that those responsible for the registration of chemicals, both on the side of the industry and on the side of the authorities, are adequately trained toxicologists. In addition, the waiving of tests should be fostered by the setting-up and implementation of concrete waiving strategies.

### Waiving strategies

A few concrete waiving strategies have already been set up for specific purposes with the aim of avoiding unnecessary testing, and some of these have reached the level of the Organization for Economic Cooperation and Development (OECD) acceptance. For example, the OECD (11) has laid down that "possible skin corrosion has to be evaluated prior to consideration of eye irritation/corrosion in order to avoid testing for local effects on eyes with skin corrosive substances".

Detailed waiving strategies for all relevant endpoints should be laid down along these lines, also taking into account different data requirements for different classes of chemicals and different exposure scenarios. When deciding which data to collect for the registration of a specific chemical, the aim of the data gathering should always be kept in mind. In the end, information is gathered with the purpose of enabling classification of a chemical substance according to its expected hazard; necessary restrictions in the use of the substance are laid down according to the respective classification. The restrictions implemented for the so-called CMR substances, chemicals that are carcinogenic, mutagenic or toxic for reproduction, are especially strict.

In the following, a concept is proposed on how to classify CMR substances while avoiding animal testing. First, the substance should be tested *in vitro* in a point mutation and a cytogenetics assay. If the substance is negative in both of these tests, it

should be tested in a further *in vitro* assay, which should include aneuploidy as an endpoint. In order to find those substances that only become mutagenic after metabolic activation, it is important to add a relevant metabolically active component to the test system (see also, 12). In order to avoid animal testing, *in vivo* mutagenicity tests should not be performed. Instead, substances should be classified as mutagenic if they test positive in a relevant *in vitro* mutagenicity test. Furthermore, mutagenic substances should be considered to be carcinogenic without further testing, since genotoxicity is a starting point for the development of cancer. Only if a substance is not found to be genotoxic should carcinogenicity testing be considered, and suitable *in vitro* tests should be developed and validated for this purpose. Reproduction toxicity tests should not be performed if a substance has been found to be genotoxic or carcinogenic. The outcome of the testing of that endpoint would be irrelevant for the classification of the substance, which has already been classified as CMR.

### Avoidance of duplication of testing

Chapter 2.1 of the White Paper states that: "Existing substances amount to more than 99% of the total volume of all substances on the market" and that "there is a general lack of knowledge about the properties and the uses of existing substances". To overcome this knowledge gap, Chapter 4 of the White Paper calls for the establishment of a single coherent system of chemicals control. All chemicals produced will have to undergo the process of registration. Taking into regard their production volume and level of concern, they might also be subject to evaluation and authorisation. This means that the vast majority of substances that will be submitted to the new system in the coming years will be substances that already have been on the market for many years.

In the White Paper, it is also acknowledged that the lack of information on these existing chemicals might really be a lack of publicly available knowledge. *Action 3A* of the White Paper recommends that: "The available information should be thoroughly examined and best use made of it in order to waive testing, wherever appropriate". Additionally, *Action 5F* of the White Paper requests that: "Specific provisions should be included in the legislation that duplicate tests involving vertebrate animals should be avoided. Any duplicate testing will not result in an exemption from the duty to reimburse the party who owns the property rights for the first test".

It is unlikely that industry would have no information on the hazardous properties of substances that they have been using for many years. Therefore, the implementation of the discouragement of duplicate testing in the new EU chemicals legislation is of utmost importance to ensure that all existing informa-

tion has been made use of when the former existing substances — that oftentimes are being used by different companies simultaneously — are submitted to the new system. However, such legislation will also remain important after all of these substances have undergone the REACH system. In any case, the ultimate goal for the animal welfare movement is to strive for an abandonment of all animal testing. However, the avoidance of duplicate testing should continue to be encouraged indefinitely, even if only for economic reasons.

Currently, the avoidance of duplicate testing is not mandatory at the EU level. Only two EU Member States, Austria and Germany, have enforced such a clause in their respective national legislations. For example, *Article 20a* of the *German Chemicals Act* (13) states that a company has to ask the notifying authority whether a test with vertebrate animals is unavoidable before it performs any animal tests for the preparation of a notification. Data from previous animal tests have to be used. The property rights of the party who performed the test in the first place are ensured by the legal duty of the second party to reimburse the first party. In addition, the second party has to withhold the notification of the chemical for the period it would have taken to perform the animal test in question.

Such a legally based discouragement of duplication of testing will prevent even more animal tests when implemented on an international level. The respective article in the revised EU chemicals legislation should be sufficiently detailed to ensure an effective avoidance of duplicate testing. Before the performance of any animal testing for a given purpose is considered, industry should be requested to ask the registration authority whether data for the registration of the substance under consideration already exist. In case an approval system for animal experiments is in force in the respective Member State, industry should be requested to forward a written confirmation to the responsible animal testing approval authority, stating that data on the respective substance do not yet exist.

The European registration authorities must run a joint database on animal tests, which should also cover ongoing animal tests to avoid accidental duplication of ongoing testing. At best, this database would also encompass tests performed during research and development. However, since this is a phase that is likely to be exempted from the full REACH system, this latter demand might not seem feasible. Thus, in order to prevent duplicate toxicity testing from taking place during research and development, legal ways should be found to discourage the performance of *in vivo* toxicity tests during that phase.

### **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. ECVAM, the European Centre for the Validation of Alternative Methods of the Joint Research Centre of the European Commission, has published a report, in which the current status of alternative methods for all relevant toxicity test endpoints is depicted (12). For each endpoint, recommendations are given on how to use existing alternatives and how to promote the development of further alternative methods. These recommendations 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 development and validation.

In the White Paper, concrete deadlines for the registration of chemicals have been set. 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. Additionally, 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 be a priority key action in the Sixth EU Framework Programme for Research. The Environment Council has explicitly formulated this request, and reference is made to it in the European Parliament Resolution.

In preparation of the research programme, the European Commission has invited scientists to submit Expressions of Interest on 20 March 2002. This invitation closed on 7 June 2002. The Expression of Interests initiative is providing the Commission with input for preparing the relevant Work Programme, as well as defining the scope of the first calls for proposals. The evaluation of all Expressions of Interests is reported on <http://www.cordis.lu/fp6/eoi-analysis/htm>. In document 1.1.1 of this website (14), it is stated that research actions in the thematic priority “life sciences, genomics and biotechnology for health” will encompass the “development of new *in vitro* tests to replace animal experimentation”. It is laid down that “priority will be given to alternative methods developed that will reach the level of maturity for subsequent formal validation and wide industrial and economic application”. Since however, it is not specifically mentioned that alternative methods shall be developed for the testing of chemicals and since the priority of alternative method development has not received a distinct concrete budget, it remains to be seen how successful this research action will turn out to be.

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 Environment Council's request that the European Commission should play a more active role on the level of the OECD should be given careful consideration.

## Conclusion

In the European Commission's White Paper on a *Strategy for a Future Chemicals Policy*, 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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