Institute for Environment and Health

TESTING REQUIREMENTS FOR PROPOSALS UNDER THE EC WHITE PAPER 'STRATEGY FOR A FUTURE CHEMICALS POLICY'

IEH Web Report W6

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This report was prepared by the Institute for Environment and Health for the Department of the Environment, Transport and the Regions and issued to the Department in April 2001. The purpose of the report has been to inform policy development in relation to proposals in the European Commission White Paper '*Strategy for a Future Chemicals Policy*'.

The views expressed here do not necessarily represent those of any government department or agency.

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A response by Dr LS Levy (OBE) on behalf of the MRC Institute for Environment and Health to the House of Lords European Union Committee (Sub-Committee D) on the European Commission White Paper 'Strategy for a Future Chemicals Policy' can be found at: http://www.le.ac.uk/ieh/update/update.html

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Executive summary

The recent European Commission (EC) White Paper *'Strategy for a Future Chemicals Policy'* outlines a framework to ensure that approximately 30 000 substances will have been tested and evaluated by 2012 at a cost, predicted by the EC, of €2.1 billion. These proposals were made in the light of growing concerns about the slow progress being made in the assessment of risks associated with 'existing substances' in use in Europe today, for the majority of which there are few or no data relating to mammalian or environmental toxicity.

The then UK Department of the Environment, Transport and the Regions (DETR) commissioned this report to address concerns about the feasibility of achieving the EC's strategy within the timeframe proposed, and also to verify whether the projections made in the EC White Paper about the capacity of the Europe-based contract research organisations (CROs) that would undertake this work are realistic. The report also addresses the financial costs and animal use involved in meeting the proposals set out in the EC White Paper. The calculations and estimates in the report are based on a number of assumptions and uncertainties. For example, the estimates regarding CRO capacity are based on current information and take no account of possible future increases in capacity. The estimates of the numbers of animals that would be used to achieve the EC proposals are based on theoretical minimum numbers (applied across all substances) rather than on the numbers that would be used in practice. Because chemicals tend to be tested on a case-by-case basis, the actual animal numbers used for testing purposes will vary from substance to substance.

Overall, 24 CROs were contacted in a survey conducted by the MRC Institute for Environment and Health (IEH), requesting information about, time, cost and annual resources required for toxicity testing. Of the CROs contacted, 16 stated that they undertake regulatory testing of industrial chemicals; 4 of the 16 have two or more testing facilities in Europe and 5 are single-site operations; no information is available about the number of site facilities of the other 7. Seven CROs provided detailed information on testing capacity for the three testing levels currently defined by the European Union (EU). It is believed that these CROs provided a fairly representative picture of European activity in the field of industrial chemical testing. The consensus from the survey was that Base set testing takes approximately 8 months per chemical to complete, Level 1 testing takes up to 1 year and Level 2 testing up to 2.5 years.

Based on calculations of the current capacity of Europe-based CROs, as identified in the survey and assuming no increase in future capacity, it is apparent that facilities for achieving the EC strategy in the proposed time-scales are not available. Calculations for testing 30 000 substances at current capacity rates suggest that there would be a 77% shortfall for Base set, a 70% shortfall for Level 1 and a 76% shortfall for Level 2 testing within the proposed EC time-scales. Again, assuming no increase in current capacity for chemical testing, the time-scales proposed by the EC would need to be extended by 36 years, to 2048, for Base set, 16 years, to 2024, for Level 1, and 13 years, to 2018, for Level 2. However, if alternative proposals to reduce the number of substances that require Base set testing from 30 000 to 10 000 chemicals (based a proposed change to increase the level at which Base set testing is required from production volumes of 1 tonne per year to 10 tonnes per year) were to be adopted, the time-scale for the completion of Base set testing, only, could potentially be reduced to 2017.

The results of the survey also indicate that financial cost involved in the proposed strategy has been greatly underestimated by the EC. Financial estimations based on the information received from the CROs put the cost of the proposed strategy at €8.68 billion[a] for 30 000 chemicals. Even allowing for a 25% reduction in the number of chemicals requiring testing (on the assumption that this proportion of the total number of substances already have sufficient toxicity data) the cost would be €6.51 billion. These costs would be increased by any addition to the current test batteries, for example to address concerns about endocrine disruption and neurotoxicity, and also by inflationary trends.

In the EC White Paper, the number of animals that would be used in chemical toxicity testing to achieve the goals of the proposed strategy was not discussed. Calculations made here suggest that 12.8 million animals[b] (8.4 million mammals and 4.4 million fish) will be required for the testing of 30 000 substances, or approximately 9.58 million for the testing of 22 500 substances (assuming a 25% reduction in the number of chemicals that require testing). These numbers are substantially increased if the offspring produced in reproductive studies and animals used in some higher tier tests are taken into account. In addition, inclusion of novel tests for mammalian neurotoxicity and endocrine disruption would further increase the number of animals required.

These considerations clearly call into question the feasibility of achieving the EC's proposed strategy.

[a] Billion is defined as 10^9

[b] Estimated animal numbers refer to vertebrates only

1 Introduction

The European Commission (EC) White Paper *'Strategy for a Future Chemicals Policy'* (CEC, 2001) was produced in response to concerns that progress in the risk assessment of existing substances under current legislation is slow and as a consequence is not affording sufficient protection to human health and the environment. The principal legislative instrument for the control of chemical substances in the European Union (EU) is the Dangerous Substances Directive (EEC, 1967), which sets out provisions for classifying, packaging and labelling dangerous substances. This Directive has undergone numerous amendments; the 'sixth amendment' (now replaced by a 'seventh amendment') introduced a prior notification scheme for new substances (i.e. those placed on the market since 18 September 1981). Under this scheme, manufacturers are required to evaluate the potential harmful effects of a new chemical prior to its marketing and use. The extent to which the risks are evaluated depends on the chemicals' production/import volume. The 'sixth amendment' also established a basis for EC legislation on the control of existing substances (placed on the market before 18 September 1981). Currently these are controlled under the Existing Substances Regulation (EEC, 1993), which places an obligation on manufacturers and importers who make or import certain quantities of existing substances to provide the EC with existing data relevant for a risk evaluation. These data are used to prioritise chemicals that require detailed risk evaluations, which are conducted at Member State level. The scheme for assessing the risks associated with existing substances has been criticised for making slow progress and for a lack of commitment and resources from Member States and industry.

Other important legislative instruments relating to the control of harmful substances include the Dangerous Preparations Directive (EC, 1999), which requires an assessment of risks to health and the environment to be made in relation to mixtures or solutions of two or more substances. This Directive compliments the 'seventh amendment' to the Dangerous Substances Directive and consolidates previous legislation on the classification, labelling and packaging of preparations. The marketing and use of substances and preparations are controlled under the Dangerous Substances and Preparations Directive (EEC, 1976), which has been amended or adapted many times to extend restrictions on certain substances or to reflect technical progress.

In addition to the slow progress being made in the assessment of existing substances, concerns about the current regulatory regime have arisen, fuelled by potential human health and environmental issues, like the rise in the incidence of certain cancer types, and endocrine disruption associated with environmental exposure to substances such as industrial chemicals (e.g. halogenated organic compounds). In response to this, the EC undertook a review of current policy on chemicals and decided that revision was necessary to ensure a high level of protection to human health and the environment. The resulting document, released in February 2001, outlines a new strategy to deal with both existing and new substances under a single system, 'REACH' (Registration, Evaluation and Authorisation of CHemicals). The proposed approach requires the testing of all existing substances that are produced and/or imported in volumes exceeding 1 tonne (approximately 30 000 chemicals) to have been completed by 2012 at a predicted cost of €2.1 billion[*].

The MRC Institute for Environment and Health (IEH) was commissioned by the then Department of the Environment, Transport and the Regions (DETR) to undertake an assessment of whether the objectives of the EC White Paper are achievable and/or realistic, given the scope of the task involved. The aims of this assessment are to:

- inform UK negotiations for Council conclusions on the EC White Paper;
- specify the capacity to meet the testing requirements necessary to achieve the deadlines envisaged in the EC White Paper;
- identify current testing resources within the EU;
- identify a realistic time-scale to undertake the proposed testing regime for Base set, Level 1 and Level 2;
- assess whether testing resources are likely to be sufficient to achieve the proposed deadline in the EC White Paper; and
- provide broad estimates of the animal testing and cost implications of the EC proposals.

[*] Alternative proposals have also been made in the EC White Paper to reduce the number of substances that need to undergo Base set testing from 30 000 to 10 000. Under this scheme, the production/import volume that triggers the requirement for Base set testing would be raised from 1 tonne to 10 tonnes.

2 Methodology

2.1 SURVEY OF CONTRACT RESEARCH ORGANISATIONS IN EUROPE

To gather the data required to undertake an assessment of the feasibility of achieving the objects of the EC White Paper, IEH conducted a survey of European Contract Research Organisations (CROs). The selection criteria for making contact with CROs were that the CRO was located in the European Economic Area (EEA) and that it undertook either ecotoxicity, mammalian or full regulatory testing of industrial chemicals. An initial list was developed from personal contacts in contract research, membership lists of societies such as the British Toxicology Society, and searches on the World Wide Web. Organisations that were able to undertake the full battery of tests or those with the capability of undertaking mammalian tests were contacted. Using these criteria, 24 Europe-based CROs were identified and contacted.

Appropriate contact names for people within each of these organisations were identified from either the company Web Site, by telephone or via email; at this point it was confirmed that the organisations did indeed undertake regulatory testing of industrial chemicals. A questionnaire* was then faxed to all those that had responded positively, requesting the following information on capacities for conducting Base set, Level 1 and Level 2 tests (the mammalian and ecotoxicity test packages currently defined by the EU).

- The time taken for a chemical to complete testing at each level
- The approximate cost for a chemical to complete testing at each level
- The number of animals (vertebrates) required for testing at each level
- The number of chemicals that the company would be able to test per year at each of the testing levels

Information was requested in terms of a) total capacity, and b) predicted available capacity (i.e. allowing for normal predicted work on new substances). Where the company had laboratories elsewhere in the world, information was requested separately about a)

* A sample questionnaire letter is shown in Annex 1 and a letter of introduction from DETR is given in Annex 2.

laboratories in Europe, and b) total capacity worldwide. Information provided by CROs about their capacity outside Europe was limited and is therefore not discussed further.

In addition, information was requested regarding the capacity to perform the screening information data set (SIDS) reproductive toxicity study, since the inclusion of this test may possibly become an additional EU requirement. Information provided by the CROs about their capacity to perform SIDS reproductive toxicity tests was limited and as a consequence is not discussed further.

Companies that had not replied by 21 March 2001 were recontacted by telephone and email on 3 and 4 April 2001. Responses received after the 16 April, 2001 were disregarded.

2.2 TREATMENT OF DATA

Chemical numbers

The EC White Paper states that there are 30 000 chemicals yet to be assessed under the Existing Substances Regulation. Estimates of the numbers of these chemicals that require testing at Level 1 (produced/imported in quantities between 100–1000 tonnes) and Level 2 (produced/imported on quantities above 10 000 tonnes) were provided by DETR; it was estimated that 5592 chemicals require testing at Level 1 and 2617 at Level 2.

Calculations were also undertaken, at the request of DETR, using the assumption that adequate data are already available for 25% of the chemicals and that these chemicals will not require further testing. This provided the basis for calculations assuming a 'worst case' scenario, where all chemicals require testing and a 'best case' scenario where only 75% (i.e. 22 500) of these chemicals need testing. Worst and best case scenarios were also derived, similarly, for chemicals requiring Level 1 and Level 2 testing, based on DETR estimates.

Finally, additional calculations were made to take amount of alternative proposals, made in the EC White Paper, to reduce the number of chemicals that need to undergo Base set testing, by requiring such testing only for those chemicals produced/imported in quantities above 10 tonnes. This would reduce the number of chemicals to be tested from 30 000 to 10 000.

Capacity

The available capacity of European CROs was derived from the median capacity of the CROs that replied to the survey. There was a wide variation in capacity reported by the CROs for

each test level. The median capacity was multiplied by the number of European CROs that can undertake the full battery of tests for industrial chemicals (n = 16), irrespective of the number of sites within the EEA or worldwide.

Animal numbers

Initial responses from the CROs indicated a considerable variability in animal numbers used for Base set, Level 1 and Level 2 testing. It was therefore decided to adopt a consistent approach to the calculations for each test level by using the following criteria.

- A standardised scenario was applied with regard to the number and type of toxicity tests according to the Notification of New Substances (NONS) requirements and the Organisation for Economic Cooperation and Development (OECD) guidelines. No allowance was made for the possible combination of tests (e.g. combining carcinogenicity and chronic toxicity studies).
- The predicted number of animals required for each toxicity test reflected the absolute minimum requirement for that test (based on OECD guidelines).
- Certain specified tests were disregarded if their use was only rarely needed (e.g. in vivo mutagenicity tests) or was not possible to predict (e.g. mechanistic investigations).

The details of the tests required for each level were obtained from the UK Health and Safety Executive (HSE) Web Site[*], as it was considered that this would represent a complete and up-to-date source of information on regulatory requirements for NONS testing and thus for testing existing substances (as proposed in the EC White Paper). The EC testing requirements listed under Base set, Level 1 and Level 2 were then considered together with the OECD test assessment guidelines (OECD, 2001) for toxicity tests, and a table was compiled of the tests and the minimum number of animals required for each test (assuming current OECD guidelines, vertebrates only; see Annex 3).

The number of chemicals that need to be tested was multiplied by the estimated theoretical minimum number of animals for each test level. This gave the estimated minimum number of animals required to achieve the EC White Paper objectives.

[*] Notification of new substances, available [March 2001] at http://www.hse.gov.uk/hthdir/noframes/nons/nons1.htm

Costs

The monetary cost of testing the proposed number of chemicals was derived by calculating the required numbers of chemicals that need testing (as outlined above), again providing the worst and best case scenarios, and multiplying these with the cost figures provided by the CROs. When costs were given in local currency, a web-based currency calculator[a] was used to calculate the cost in Euros (€). Each CRO provided a range of costs for chemical testing. The lowest end of the range from each CRO was used to derive a median cost for test packages[b]. These values were used as the basis for the cost calculations presented in this report.

Time-scales

The number of substances that could be tested within the proposed EC time-scale was calculated by multiplying the total chemical testing capacity per annum by the number of years up to the proposed EC deadline (2012 — 11 years for Base set; 2008 — 7 years for Level 1; 2005 — 4 years for Level 2). These calculations assume no increase in the current capacity for chemical testing. More realistic time-scales were then calculated by dividing the number of substances requiring testing by the current yearly European capacity for testing chemicals. This gave the number of years required to test the numbers of chemicals proposed according to the three scenarios (i.e. all chemicals at the appropriate test level, only 75% of the chemicals assigned to each level or a reduction in Base set testing numbers to only 10 000). These figures were then added to the current year (2001) to give the year by which all testing could be completed, assuming that there would be no increase in current testing capacities and that testing would start at the end of 2001.

2.3 ASSUMPTIONS AND UNCERTAINTIES

Of the CROs that responded to the survey, 58% were from single site facilities and 42% from companies consisting of two or more facilities. It is believed that the sample gave a fairly representative cross-section of CRO facilities and capacities within the EEA (see section 3.1). The responses received indicated that there were many uncertainties involved in providing the requested information, and therefore several assumptions were necessary to complete this study.

[a] http://www.x-rates.com/calculator.html
[b] Test packages include vertebrate, invertebrate toxicity and physicochemical studies

The calculations provided in this report are based on estimates produced by the EC concerning the number of chemicals that would require testing. As outlined above, it is believed that, at worst, 30 000 substances and, at best, 22 500 substances would require testing. The estimates of the number of chemicals that would be tested at Level 1 (5592) and Level 2 (2617) were provided by the UK DETR. In addition the report provides calculations to reflect alternative EC proposals to reduce the number of substances that need to undergo Base set testing from 30 000 to 10 000 chemicals. No attempt has been made in these calculations to address the uncertainties regarding the alternative proposal, such as how the remaining 20 000 chemicals (that would fall out of the proposed system) would be dealt with.

The current EC test requirements (as listed by the UK HSE), in conjunction with the OECD test protocol guidelines (which are internationally recognised and largely accepted globally) were used as a basis for calculations. The numbers of animals used in the calculations presented here represent the theoretical minimum numbers of animals based on these requirements and guidelines. As data from the CROs have implied, these numbers can be greater or smaller depending on the chemical under investigation. An example of this is the reproductive screening test in the Base set, which is a requirement under EC regulations (and is therefore included in the calculations) although it is rarely undertaken in practice.

It is acknowledged that the EC White Paper proposes that the requirements for Base set testing should be modified to comprise, generally, only *in vitro* models[*]. However, no details are given on the proposed modifications and there is no consensus that alternative *in vitro* models are yet available to replace currently required *in vivo* tests. This being the case, the possible implications of the proposed modifications have not been allowed for in the estimates of annual numbers presented herein.

Only tests using vertebrate animals were considered when calculating animal use; offspring from reproductive studies were disregarded from the main calculations owing to the uncertainties of experimental design and number of offspring produced. It is possible that further tests may be added to EU requirements in the future, such as mammalian neurotoxicity and endocrine disruption screening tests. The extent to which these will impact on the projected number of vertebrate animals is presently unknown. Higher tier tests such as avian toxicity, *in vivo* mutagenicity and mechanistic toxicity studies have been disregarded,

[*] EC White Paper, Sections 3.1, Action 3B

as these are only undertaken based on positive results from lower tier tests, rather than on chemical production volume, as required by the EC White Paper.

When assessing capacity, it was assumed that all CROs in the EEA possessed the median capacity reported by the seven CROs who responded to the survey (see section 3). It was assumed that the lower capacities of smaller independent CROs would be counter-balanced by the larger CROs. This assumption was based on the premise that the larger CROs have several sites and capacity could potentially be increased in line with demand (although the exact details were not provided and thus future increases in capacity are unpredictable). Capacity calculations were used to estimate the feasibility of achieving the time-scales proposed in the EC White Paper. Calculations, based on information provided by the CROs, were made to identify the number of chemicals that could be tested within the time-scales. From these, extrapolations were made to identify more realistic deadlines. In making these estimates, no allowance was made for the possibility of future increases in CRO capacities within Europe or for the possibility that such work could be undertaken outside Europe, although it is recognised that these are distinct options, owing to the globalisation of the contract research business.

No allowance has been made in the calculations for the need for individual chemicals to be progressed along the test levels in sequence, with consequent implications for the times at which a chemical could enter the higher testing levels. The time needed to test a chemical at all levels is not, in reality, the sum of the individual durations for each level (i.e. Base set — 8 months, Level 1 — 1 year, and Level 2 — 2.5 years; total of 4 years 2 months). However, the need to undertake certain complex and/or longer toxicity tests is sometimes determined by the results of the lower level studies.

The majority of CROs that responded to the survey provided a range of costs for each test level, either in the form of the cost for each individual toxicity study or for complete toxicity test packages (the latter including the costs for each level including physicochemical property data, chemical fate and behaviour, mammalian toxicity, ecotoxicity, dossier production and registration). The median of the lower-end costings for test packages was used in the calculations. It is important to note that the costs cited in this report do not take into consideration the additional regulatory costs of risk assessments by raporteur countries nor the assessment of these reports by other EU countries, and there is no allowance for the effects of inflation.

3 Results

3.1 SURVEY RESULTS

Of the 24 Europe-based CROs contacted, seven qualifying CROs replied to the survey, five indicated that they do not undertake regulatory testing for industrial chemicals, five failed to respond or to take part, and a further four failed to reply within the required deadline. Three CROs undertook only ecotoxicological tests and were therefore omitted from further consideration. The survey has established that there are currently 16 Europe-based CROs that undertake the battery of toxicity tests required by EC legislation. No data regarding testing capacity outside Europe were provided. Calculations made in the body of this report are based on the seven formal responses received within the required time-scale of the study.

The responses to the questions about the number of studies undertaken per year and the number of sites indicated a wide range of capacities between the different CROs. Of the seven CROs that participated in the survey, four (58%) are single site operations whereas three (42%) have two or more sites within the EEA that undertake the testing of industrial chemicals. Of the single site operations, three were relatively small, with a capacity to undertake 10 to 15 Base set studies per year and one was of medium size and able to undertake 36 such studies. The other three CROs were able to undertake 50 to 100 Base set studies per year, and two stated that capacity could be increased if required. Therefore, although only seven CROs participated in the survey, the responses cover a wide range of testing capacities.

While taking into account the caveats regarding capacities, costs and animal numbers, this survey is deemed to be fairly representative.

3.2 CAPACITY REQUIRED TO CONDUCT TESTS

Information received from testing houses suggests that, on average, each Base set test would take up to 8 months to complete per chemical, Level 1 tests would take up to 1 year, and Level 2 tests up to 2.5 years. Assuming that the 16 European testing houses would undertake the work, the number of chemicals that would need to be tested every year to achieve the target schedule proposed by the EC, and the average number of chemicals that each European testing house would need to complete each year are shown in Table 1.

Table 1 Required testing house capacity

Level: Number of chemicals	Required annual throughput (chemicals per year)	Required throughput (chemicals per laboratory per annum)
Base set: 30 000 chemicals	2727 up to 2012	171 up to 2012
(75%): 22 500 chemicals	2045 up to 2012	128 up to 2012
10 000 chemicals	909 up to 2012	57 up to 2012
Level 1: 5592 chemicals	799 up to 2008	50 up to 2008
(75%): 4194 chemicals	599 up to 2008	37 up to 2008
Level 2: 2617 chemicals	654 up to 2005	41 up to 2005
(75%): 1963 chemicals	491 up to 2005	31 up to 2005

3.3 ESTIMATED TESTING CAPACITY IN EUROPE

Based on the current available capacities reported by the individual European testing houses, the 'best case' scenario for the number of chemicals that could be tested per year, and the predicted annual shortfall (based on the EC proposals) are shown in Table 2.

Table 2 Estimated European testing house capacity

Level: Number of chemicals	Proposed EC deadline	Current annual capacity per testing house	Annual capacity shortfall per CRO*
Base set: 30 000 chemicals	2012	40 chemicals	130 chemicals
(75%): 22 500 chemicals			88 chemicals
10 000 chemicals			17 chemicals
Level 1: 5592 chemicals	2008	15 chemicals	35 chemicals
(75%): 4194 chemicals			22 chemicals
Level 2: 2617 chemicals	2005	10 chemicals	31 chemicals
(75%): 1963 chemicals			21 chemicals

* Based on estimated current capacity of the 16 European CROs that undertake the full test battery.

3.4 NUMBER OF ANIMALS

Table 3 details the minimum number of vertebrates (mammals and fish) that would be required to test either all 30 000 substances or 75% of them, according to current OECD study requirements for Base set, Level 1 and Level 2 (see Annex 3). It should be noted that animal numbers provided by CROs for a Base set test where somewhat lower than those based on the OECD requirements (CROs 133–202; based on OECD requirements 210).

Table 3 Numbers of animals required (vertebrates)

Level: Number of chemicals	Number of animals per chemical		Total number of animals for all chemicals (millions)		
	Mammals	**Fish**	**Mammals**	**Fish**	**Total**
Base set: 30 000 chemicals	168	42	5.040	1.260	6.300
(75%): 22 500 chemicals			3.780	0.945	4.725
10 000 chemicals			1.680	0.420	2.100
Level 1: 5592 chemicals	240	362	1.342	2.024	3.366
(75%): 4194 chemicals			1.006	1.518	2.524
Level 2: 2617 chemicals	768	420	2.009	1.099	3.108
(75%): 1963 chemicals			1.508	0.824	2.332

The number of mammals and fish required for testing all 30 000 chemicals is 12 774 000, and for testing 75% of these chemicals is 9 581 000.

If the numbers of offspring produced during mammalian reproductive studies are included then, based on a tentative assumption that each female mammal would produce ten offspring per litter, the number of mammals used for testing 30 000 chemicals would increase from 8.4 million to around 45.8 million

Should the requirement for undertaking Base set testing be reduced to 10 000 chemicals (instead of 30 000) the number of mammals and fish required for testing would be 8 574 000 assuming current test protocols remain unchanged.

3.5 FINANCIAL COST OF THE PROPOSED EC STRATEGY

The following estimate of financial cost (Table 4) is derived from the current median price for completion of a testing package (i.e. including physicochemical data, chemical fate and behaviour, mammalian toxicity and ecotoxicity).

Table 4 Financial cost of the proposed EC strategy

Level: Number of chemicals	Cost per chemical (€ million)	Total cost (€ billion)
Base set: 30 000 chemicals	0.12	3.600
(75%): 22 500 chemicals		2.700
10 000 chemicals		1.200
Level 1: 5592 chemicals	0.3	1.678
(75%): 4194 chemicals		1.258
Level 2: 2617 chemicals	1.3	3.402
(75%): 1963 chemicals		2.552

The estimated total cost for testing 30 000 chemicals at Base set, 5592 at Level 1 and 2617 at Level 2 is €8.68 billion. If only 75% of chemicals at each level require testing costs are reduced to €6.51 billion.

Should the requirement for undertaking Base set testing be reduced to 10 000 chemicals instead of 30 000 the financial burden would be reduced to €6.28 billion.

3.6 FEASIBILITY OF ACHIEVING THE EC PROPOSALS

The number of chemicals that could be tested at current estimated capacity, and the consequent shortfall (in terms of meeting the proposed EC time-scales), are presented in Table 5.

Table 5 Numbers of chemicals that can be tested within the proposed EC deadlines

Level: Number of chemicals	**Cumulative number of chemicals that could be tested***	**Cumulative shortfall (Number of chemicals)**
Base set: 30 000 chemicals	7040 by 2012	22 960 by 2012
(75%): 22 500 chemicals		15 460 by 2012
10 000 chemicals		2960 by 2012
Level 1: 5592 chemicals	1680 by 2008	3912 by 2008
(75%): 4194 chemicals		2514 by 2008
Level 2: 2617 chemicals	640 by 2005	1977 by 2005
(75%): 1963 chemicals		1323 by 2005

* Based on estimated current capacity of the 16 European CROs that undertake the full test battery

Based on the same estimate of current capacity (and assuming no increase in future capacity), the earliest time-scales for the completion of testing of all 30 000 chemicals or of 75% of these are shown in Table 6.

Table 6 Time-scales achievable using current capacity

Level: Number of chemicals	Total chemical testing capacity per annum*	Proposed EC deadline	Achievable deadline
Base set: 30 000 chemicals	640	2012	2048
(75%): 22 500 chemicals			2036
10 000 chemicals			2017
Level 1: 5592 chemicals	240	2008	2024
(75%): 4194 chemicals			2019
Level 2: 2617 chemicals	160	2005	2018
(75%): 1963 chemicals			2013

* Based on estimated current capacity of the 16 European CROs that undertake the full test battery

4 Discussion

This survey has shown that there are only a few CROs in Europe capable of undertaking regulatory testing of industrial chemicals. From the seven that responded to the survey, a clear cross-section of CRO activity in relation to industrial chemicals was identified. Several companies had difficulty in providing the exact information requested (e.g. in relation to costs, animal numbers and capacity) because requirements at each level of testing vary, as individual chemicals are treated on a case-by-case basis. It also became apparent from communications with the CROs that there was considerable uncertainty concerning the proposed regulatory changes and the impact that this would have on their activities. In addition, there appeared to be a lack of consultation between the EC and the CROs during the preparation of the EC White Paper. This is reflected in the discrepancy, highlighted during this study, between the number of chemicals requiring testing in the EC White Paper and the capacity of the CROs to test them.

The number of animals required to meet the EC proposals was not addressed in the EC White Paper. Although a commitment to reducing the use of animals through novel testing regimes was made, the proposed time-scale for chemical testing appears to be insufficient to allow the validation of new tests. From the calculations of number of chemicals, the type and number of tests per level required by the EC regulations for registration, and the experimental regimes taken from the current OECD guidelines, it was estimated that the number of vertebrate animals required to complete the EC's strategy would be in excess of 12 million for testing 30 000 chemicals. Even assuming that 25% of the chemicals will not require any form of testing, the estimated number of animals remains in excess of 9 million. These numbers exclude offspring from reproductive studies and the use of animals in avian studies, invertebrate tests and higher tier toxicity tests, such as mechanistic toxicity studies and *in vivo* mutagenicity studies. The calculations, based on OECD guidelines for experimental design, are greater for Base set levels than the figures provided by the CROs. Animal numbers provided by the CROs for a Base set test ranged from 133 to 202 (our calculations are based on 210)[*]. Owing to difficulties with predicting animal numbers for Level 1 and

[*] The discrepancy between the calculated animal numbers for Base set in this report and the figures provided by the CROs arises because not all the tests as specified under the legislation are carried out in practice. In addition, a number of different protocols are used for acute toxicity tests.

Level 2 tests, the CROs did not provide an estimation of numbers of animals used in these tests.

There appears to be a gross underestimation of the financial cost in the EC White Paper. The survey of the CROs provided a range of costs that varied according to differences in testing requirements for individual chemicals. The median costs for Base set and Level 2 were much greater than those estimated in the White Paper, although the cost for Level 1 testing was similar. Overall, there appears to be an approximate three-fold underestimation of cost by the EC in relation to the testing of 30 000 substances (EC proposed €2.1 billion; calculated €8.68 billion). The actual cost would rise with inflation, and can also be expected to increase with future additions to regulatory requirements (e.g. endocrine disruption and neurotoxicity tests).

The EC's proposals with regard to budget and time-scale are unrealistic, given the scale of new testing that would be required. Based on the CRO survey, at current operating rates, there would be a considerable shortfall in the number of chemicals tested at each test level compared with the EC proposals. However, two CROs stated that operating rates could be increased if there was a market need to do so; therefore, the number of chemicals that could be tested by the deadlines could be increased. However, owing to a lack of information any increase in future capacity remains uncertain. Based on the calculations for testing 30 000 substances at current capacity rates, it is estimated that there would be a 77% shortfall for Base set testing, a 70% shortfall for Level 1 testing and a 76% shortfall for Level 2 testing within the proposed EC time-scales. At current operating rates (assuming no future increase in capacity), more realistic deadlines for testing 30 000 substances in Base set, Level 1 and Level 2 tests would be 2048, 2024 and 2018, respectively. One consequence of extending the time-scales to this extent would be to provide an opportunity for the development and validation of *in vitro* models to replace some of the current *in vivo* tests; this would result in a reduction in the numbers of animals used and, potentially, financial savings through the use of less expensive methods. However, if alternative proposals are adopted to reduce the number of substances that need to undergo Base set testing from 30 000 to 10 000, the time-scale for the completion of Base set testing, only, could potentially be reduced to 2017.

5 Conclusions

- The estimated total cost of testing 30 000 substances in line with the EC proposals would be around €8.68 billion and would require at least 12 million vertebrates (8.4 million mammals and 4.4 million fish). These calculations exclude offspring produced during reproductive toxicity studies, any necessary avian testing and animals used in the higher tier toxicity tests.
- It is estimated that the testing facilities in Europe alone do not currently have sufficient capacity to meet the proposed schedules for testing. It is estimated that there will be a shortfall of approximately 75% of the required testing by the proposed target end dates (assuming no future increases in capacity).
- Based on current estimates of European capacity (assuming no increases in future capacity), achievable target dates for the completion of testing at the various tiers are: 2048 for Base set testing for 30 000 chemicals; 2024 for Level 1 testing; and 2018 for Level 2 testing. However, if alternative proposals are adopted to reduce the number of chemicals that need to undergo Base set testing from 30 000 to 10 000, time-scale for the completion of Base set testing, only, could potentially be reduced to 2017.

6 Bibliography

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EEC (1976) Council Directive 76/769/EEC of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations. OJ L 262/201, 27.9.1976

OECD (2001) *Guidelines for the Testing of Chemicals* (11th Addendum), Paris, France, OECD Publications

Annex 1 Questionnaire letter

Fax Transmission

TO:		**FROM:**	Catherine Botham
AT:		**DATE:**	03 July 2001
FAX NO:		**TIME:**	
PAGES: (INCLUDING THIS ONE)	3	**REF:**	IEH 22/10a

MESSAGE

Dear

"Strategy for a Future Chemicals Policy"

I am contacting you on behalf of the UK Department of the Environment, Transport and the Regions (DETR) regarding the above-titled White Paper recently published by the European Commission (EC). As you may be aware, the EC has proposed that approximately 30 000 existing industrial chemicals should undergo evaluation over the next 12 years.

The DETR wishes to investigate the validity and implications of this proposal, in particular whether the proposed deadlines and timeframes are realistic. To accomplish this we are contacting all the major testing houses in Europe and requesting the following information on capacities for conducting Base set, Level 1 and Level 2 tests (the mammalian and ecotoxicity test packages as currently defined by the EU):

1. The time taken for a chemical to complete testing at each level.
2. The approximate cost for a chemical to complete testing at each level.
3. The number of animals (vertebrates) required for testing at each level.
4. The number of chemicals that your company would be able to test per year[*] at each of the testing levels. We would ask you to provide this information in terms of a) total capacity, and b) predicted available capacity (i.e. allowing for normal predicted work on new substances). If your company has laboratories elsewhere in the world, please give separate responses for a) your laboratories in Europe, and b) total capacity worldwide.

In addition, we would be interested to learn of your capacity to perform the SIDS reproductive toxicity study, since the inclusion of this test may possibly become an additional requirement.

[*] The EC has proposed that testing of existing chemicals should be completed by 2012.

We understand that much of this information is of a delicate and commercial nature, and therefore assure you of complete confidentiality. All replies will be treated in the strictest confidence, and will not be revealed to anyone other than DETR officials. We attach a letter of introduction from the DETR, including the names and details of DETR staff who can be contacted if you require verification on any point.

I do hope you will be able to provide the requested information, and I would appreciate a rapid reply as the Department will have to respond to the White Paper very soon.

If you require any further information, or wish to discuss any aspect, please do not hesitate to contact either Philip Holmes or myself at the above address.

I look forward to hearing from you in the near future.

Yours sincerely,

Catherine Botham
Ecotoxicologist
Email: cab15@le.ac.uk

Annex 2 Letter of introduction from DETR

SEAN RYAN
CHEMICALS AND BIOTECHNOLOGY DIVISION

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TRANSPORT AND THE REGIONS
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9 MARCH 2001

European Commission White Paper on Chemicals

The European Commission published in February a White Paper on a "Strategy for a future chemicals policy". The White Paper makes proposals for the future development of EU chemicals policy to enhance protection of the environment and human health. In particular, the White Paper proposes deadlines for the submission of hazard data on up to 30,000 chemicals currently on the market, with testing requirements that vary according to the tonnage of chemical produced or imported in the European Union.

The Government needs to consider whether the proposals and deadlines for the testing requirements in the White Paper are achievable. The Department has, therefore, asked the Medical Research Council (MRC) Institute for Environment and Health to investigate the testing implications of the proposals in the White Paper and assess their feasibility.

The Department would be very grateful for any assistance or information that you can provide to the Institute towards this study.

Should you require any further background about the study, either I or Bill Parish (0207 944 5237) would be happy to discuss it with you.

Yours faithfully

SEAN RYAN

Annex 3 Animal (vertebrate) use in Base set, Level 1 and Level 2 studies

	Time to complete	Number of test groups (minimum)	Number of animals (minimum)
Base set (for 1-100 tonnes pa)			
Acute oral toxicity – fixed dose procedure			12 per chemical
Acute dermal irritation/corrosion			3 per chemical
Acute eye irritation/corrosion			3 per chemical
Skin sensitisation			30 per chemical
Repeated dose 28-day oral toxicity study in rodents		3 + control	10 per group
Reproduction/developmental toxicity screening test		3 + control	20 per group
Total number of mammals			**168**
Acute toxicity in fish		5 + control	7 per group
Total number of fish			**42**
Total requirement for Base set	**Up to 8 months**		**210**
Level 1† (for 100–1000 tonnes pa)			
Fertility and general reproduction toxicity study		3 + control	20 per group
Teratogenicity study (rodent)		3 + control	20 per group
Repeated dose 90-day oral toxicity study		3 + control	20 per group
Total number of mammals			**240**
Bioaccumulation in fish		Approx. 4	80 per group
14-day prolonged fish toxicity		5 + control	7 per group
Total number of fish			**362**
Total requirement for Level 1	**Up to 1 year**		**602**
Level 2† (for 1000+ tonnes pa)			
Chronic toxicity studies		3 + control	40 per group
Carcinogenicity studies		3 + control	100 per group
Peri- & postnatal reproduction toxicity study		3 + control	20 per group
Teratogenicity study (non-rodent species)		3 + control	12 per group
Toxicokenetics (biotransformation & pharmacokenetics)		2 + control	20 per group
Organ or system toxicological study (additional)		Not definable	Not definable
Total number of mammals			**768**
Early life stage fish toxicity test		5 + 2 control	60 eggs
Total number of fish			**420**
Total requirement for Level 2	**Up to 2.5 years**		**1168**

† Base set, Level 1 and Level 2 tests from OECD test assessment guidelines (OECD, 2001)