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Assessment of additional testing needs under REACH

Effects of (Q)SARS, risk based testing and voluntary industry initiatives

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Risk assessment according to Aristotle:

> ***"It is the mark of an instructed mind to rest easy with the degree of precision which the nature of the subject permits and not to seek an exactness where only an approximation of the truth is possible."***

SUMMARY

A possible future chemicals legislative system was presented by DG ENTR and DG ENV in May 2003 in their REACH Consultation Document. The proposed system requires that data must be available on intrinsic properties of all substances manufactured in volumes greater than 1 tonne/year. In annexes V to VIII, data requirements depending on the volume manufactured are described together with a testing strategy, and in annex IX various rules for adaptation of the testing strategy are described.

In recent years both the lack of data on intrinsic properties of chemicals on the one hand and on the other hand the animal welfare aspects of laboratory toxicity testing for fulfilling the data requirements have caused concern. The proposed REACH system tries to deal with these concerns by introducing both the use of (Quantitative) Structure-Activity Relationships, grouping and read-across techniques, and an increased use of *in vitro* testing methods.

The current report analyses the impact of the proposed REACH system on the need for further testing in addition to already existing obligations and voluntary initiatives under various assumptions regarding the use of estimation techniques such as (Q)SARs and the outcome of screening tests and risk assessments. The impact of increased use of *in vitro* methods has not been considered, as it has not been the aim of this study to analyse the impact on the numbers of tests animals needed for the testing. The estimates are based on JRC's understanding of how the proposed testing strategy and adaptation rules will be implemented and are, furthermore, based on the general experiences obtained through more than 10 years of administration of the review programmes for new and existing chemicals under the current legislation.

However, as it is still uncertain how far estimation techniques as (Q)SARs will be developed in the coming years and consequently how far the use of such techniques will be accepted for regulatory purposes, an uncertainty analysis applying both a minimum and a maximum use of such techniques has been conducted. Uncertainties regarding the different outcomes of various tests influencing the further testing needs have also been included in this analysis.

According to the estimations, the highest numbers of tests are required for the endpoints skin sensitisation (for ~ 35% (26 – 47%) of all substances), eye irritation (~ 24% (20 – 28%) of which 5% are *in vivo* tests) and the *in vivo* mutagenicity study (~ 22%). For all other endpoints, new testing is required for less that 20% of the substances.

By combining the estimates of test needs with likely costs of individual tests, the direct testing costs in addition to existing obligations and voluntary initiatives have been estimated to 1.6 Billion EURO for the most likely scenario; however ranging from 1.2 to 2.4 Billion EURO depending on the assumptions in the uncertainty analysis. About 86% of the estimated costs of the most likely scenario will be needed for testing for human health endpoints, while only about 14% will be needed for environmental endpoints and almost nothing for development of analytical methods. It is estimated that 30% of the total testing costs will be used for development toxicity studies, 24% will be used for two-generation reproductive toxicity studies and 8% will be used for *in vivo* mutagenicity studies. Repeated dose toxicity studies including the carcinogenicity study will require in total 14% of the total testing costs.

The testing requirements and thus the costs depend on the produced quantity of a substance. In the most likely scenario, the total testing costs are distributed with 15%, 23%, 26% and 36% for substances produced in quantities of 1 – 10, 10 – 100, 100 – 1000 and > 1000 tonnes/year, respectively. Furthermore, the average testing costs per substance increases from 12000 EURO for a substance produced in a quantity of 1 – 10 tonnes/year to 208000 EURO for a substance produced in a quantity of more than 1000 tonnes/year. However, the testing costs per produced quantity of a substance are much higher for substances produced in low volumes than in high volumes with test costs distributed over 10 years decreasing from 404 EURO/tonne for a substance produced in 3 tonnes/year to only 7 EURO/tonne for a substance produced in 3000 tonnes/year.

Finally, it should be emphasised that the present estimate of testing needs and costs is based on the description of the REACH system as appearing in the REACH Consultation Document of May 2003. If the further development of the legislative text and in particular the testing strategy and the adaptation rules results in major changes, it may be necessary to update the present study.

1. INTRODUCTION

1.1 The lack of information on chemicals

In May 2003, DG ENTR and DG ENV presented their "Consultation Document concerning Registration, Evaluation, Authorisation and Restrictions of Chemicals (REACH)" (DG ENTR & DG ENV 2003) describing essential features of a new legislative system for implementing the policy set out in the Commission White Paper on a "Strategy for a future Chemicals Policy" (European Commission 2001).

The aim of REACH is to ensure that industry adequately manages the risks from its substances by obtaining adequate data, by performing chemicals safety assessments, by implementing appropriate risk management measures and by submitting a registration to the authorities. A key issue that REACH will deal with is the lack of publicly available data on chemicals. This is a problem, which has been known for at least two decades. Already in 1984 the National Research Council (1984) in the USA estimated that only 22% of the US High Production Volume Chemicals (HPVCs) had "minimal" toxicity data available. In 1990 a detailed analysis of chemicals control in the European Community showed a similar lack of information on use and toxicity of existing chemicals (Haigh & Baillie 1992). The Haigh & Baillie report also described the problem of the lack of information on downstream uses. In 1996, an international review of risk assessment of chemicals revealed the same (Van Leeuwen et al. 1996). A detailed analysis by the European Chemicals Bureau (Allanou et al. 1999) led to the same conclusion with regard to the lack of information on high production volume chemicals: only 14% of the EU HPVC had data at the level of the base-set (Directive 67/548/EEC, Annex VIIA), 65% had less than base-set and 21% had no data at all. This lack of progress in providing information to the public led to various initiatives, of which some are voluntary (e.g. the U.S. HPV Challenge Program), some are regulatory (the EU Existing Substances Regulation (EEC) No 793/93) and some are of a more horizontal nature (the OECD Existing Chemicals Programme). The lack of data on the hazardous properties of chemicals was the driving force behind the development of a new chemicals policy in the EU.

1.2 Direct testing costs

The development of the REACH legislation has now resulted in the publication of a Consultation Document (DG ENTR & DG ENV 2003) including a draft legislative text. As background for this, various studies on the possible impact of the REACH system have been carried out both on behalf of the Commission and by different stakeholders. The draft legislative text includes annexes specifying a suite of data requirements on physicochemical, toxicological and ecotoxicological endpoints for substances depending on the produced quantity as divided into four tonnage bands. In relation to this, it is seen as an issue of importance to estimate the direct impact of the REACH system on the needs for additional testing of chemicals and the possible costs of this additional testing. This has been done by RPA & Statistics Sweden (2002) in a Business Impact Study (BIS) prepared for DG ENTR. At the time of conducting this study, the possible future REACH system had not been detailed and, therefore, various scenarios were evaluated. Based on these, direct testing costs from 2.5 to 6.2 billion EURO were estimated.

Based on the results of the RPA & Statistics Sweden study, DG ENTR & DG ENV have made further estimates of the direct testing costs. Based on historical prices for testing of

chemicals and the most likely testing assumptions, they estimate the direct testing cost to be 3.6 billion EURO although it is recognised that lack of testing capacities in the EU may result in increased prices (DG ENTR & DG ENV 2003).

Various European industry associations have prepared their own assessments of the possible impact of the proposed REACH system on their business (CEFIC 2003, Arthur D. Little (2002) for the Bundesverband der Deutschen Industrie e.V. (BDI), and Mercer (2003) for Union des Industries Chimiques (UIC)). They all base their impact assessments on the findings of RPA & Statistics Sweden (2002) and, thus, they reach mainly the same results.

The study by RPA & Statistics Sweden (2002) is now being revised by RPA (draft 2003) based on the REACH system as described in the Consultation Document. In particular the impact of the acceptance of QSAR techniques has been taken into account and in their draft report, the test costs have been estimated to 3.4 and 3.5 billion EURO, respectively, for some acceptance of QSAR results and no acceptance of QSAR results (excluding costs for phase-in polymers).

1.3 Alternative approaches to animal testing and the role of the JRC

Since the publication of the Commission White Paper on a "Strategy for a future Chemicals Policy" (European Commission 2001), the Joint Research Centre (JRC) has played an active role regarding alternative (non-animal) approaches for chemical testing. Two JRC units: (1) the European Centre for the Validation of Alternative Methods (ECVAM) and (2) the European Chemicals Bureau (ECB), both part of the JRC Institute of Health and Consumer Protection (IHCP), have particular responsibilities in this respect. In this short period of time ECVAM (and the ECVAM Working Group on Chemicals) produced three important reports:

1. Alternative (non-animal) methods for chemicals testing: current status and future prospects (Worth & Balls 2002)
2. Alternatives to Animal Experiments: Progress made and Challenges Ahead (Balls 2002)
3. ECVAM response to the changing political environment for alternatives: consequences of Chemicals and Cosmetics Policies (Hartung et al. 2003)

Most importantly, these reports were developed in the international context involving the scientific and regulatory community, industry and NGOs. The conclusion is that the development, validation and regulatory implementation of *in vitro* methods are one of the approaches that could lead to a considerable reduction in the use of test animals. The programme ahead is a huge challenge. It will need adequate funding and will take at least a decade to be completed.

The second unit of the IHCP, i.e. the European Chemicals Bureau, was actively involved in the work on structure-activity relationships (SARs) and quantitative structure-activity relationships (QSARs), collectively referred to as (Q)SARs (Hansen & Van Leeuwen 1995, Karcher et al. 1995), but the activity was closed down. However, because of the increasing focus on animal welfare (use of animals for testing) and the new draft REACH legislation, ECB is again actively involved in the work on (Q)SAR. (Q)SARs are theoretical models that can be used to predict the physicochemical and biological (e.g. toxicological) properties of molecules from knowledge of chemical structure. In general, (Q)SARs are relatively "simple" models (e.g. the structural alerts that constitute SARs, or the mathematical equations that constitute

QSARs), but some "models" are actually computer programs, based on complex and integrated interactions. In principle, (Q)SARs could be used for a number of purposes in the implementation of legislation on chemical substances and products: a) to provide information for use in priority setting procedures, which are used to expedite the risk assessment process for chemicals of concern; b) to support choices made in testing strategies; c) to classify chemicals on the basis of their hazardous properties; d) to provide dose-response information; e) to provide environmental fate information; and f) to provide mechanistic information to support the interpretation of experimental data. For a further introduction into the subject reference is made to Nendza & Hermens (1995).

In the United States and Canada, (Q)SARs are used extensively for regulatory purposes. Under the current EU legislation for New and Existing Chemicals, the use of (Q)SARs is limited. This is probably mainly caused by the fact that in the EU testing information is required, especially in the case of new chemicals (Vermeire & van der Zandt 1995). In the EU, (Q)SARs have been applied for priority setting of existing chemicals, for classification and labelling (Danish EPA 2001) and for the prediction of environmental effects of HPVCs (Bol et al. 1993). However, under the future REACH system as described in the REACH Consultation Document, it is anticipated that (Q)SARs will be used more extensively, in the interests of time- and cost-effectiveness and animal welfare. In particular, (Q)SARs are likely to play an important role in the assessment of chemicals produced or imported in quantities between 1 and 10 tonnes, for which minimal animal testing is foreseen in the White Paper (European Commission 2001).

Because of these challenges, the ECB was actively involved in the organisation of the ICCA Long-Range Research Initiative Scientific workshop that took place in Setubal (Portugal) in March 2002 (Jaworska et al. 2003, Eriksson et al. 2003, Cronin et al. 2003a & 2003b). This workshop on the regulatory acceptance of (Q)SARs for human health and environmental endpoints was the start of a discussion to include (Q)SARs in the work programmes of both the Organisation of Economic Co-operation and Development (OECD) and the JRC. In November 2002, the 34th Joint Meeting (JM) of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology decided to start a new OECD activity aimed at increasing the regulatory acceptance of (Q)SARs, and to establish an *ad hoc* Expert Group for this work. The general aim of the JRC Activity on (Q)SARs, which was formally initiated on 1 January 2003, is to promote the development, validation and implementation of (Q)SARs that are useful for regulatory purposes. The JRC-IHCP will co-ordinate the practical work, due to its recognised independence from national and sectoral interests, and its established role in the provision of scientific and technical support for the development and implementation of EU legislation on chemicals. The discussion on the practical and financial involvement of industry will take place early September 2003.

It should be noted that the application of (Q)SARs is a fast-track option to deal with data gaps on chemicals. Although there is some disagreement in the scientific and regulatory community about the application of (Q)SARs, and the extent to which (Q)SARs can be relied upon, expert systems are operational. These systems are applied on a routine basis in the USA by regulatory authorities. Canada has assessed more than 23,000 chemicals in their regulatory programmes over the last two years. The Danish EPA has examined approximately 47,000 chemical substances with the aid of QSARs (Danish EPA 2001). The European Commission, through DG RTD, has funded the development of (Q)SARs in different Framework Pro

grammes over the last decade. The European Commission has evaluated the use and application of (Q)SARs in collaboration with the US-EPA (OECD 1992). Recently, an expression of interest was submitted to combine the further development and applications into one expert system for industry and regulatory communities (ECETOC 2002). So, SARs, QSARs (and related read-across and chemical category approaches) are a fast-track option to deal with data-gaps. Some work needs to be done, as (Q)SAR models as also *in vitro* methods require determination of domain and thorough validation, but (Q)SAR estimates for many endpoints can be provided for many REACH chemicals in a few years time before the actual implementation of the future REACH legislation and in particular before dossiers for the large numbers of lower production volume chemicals will have to be submitted.

Also *in vitro* methods will increasingly replace the current *in vivo* methods. Already now, ECVAM is running final validation studies, which have the potential to replace animal tests with non-expensive *in vitro* tests for the endpoints acute toxicity (may replace ~30% of animal test needs), skin irritation (~90% replacement) and occular irritancy (up to 90% replacement). As a spin-off of the developments for cosmetics and the intensified work at ECVAM, further alternatives will most likely be provided during or even before the start of REACH. However, as it is not the aim of the current study to assess the potential saving of test animals, this impact has not been considered further.

1.4 The scope of this study

The current study presents a detailed analysis of the consequences of the implementation of the future REACH legislation as described in the REACH Consultation Document (DG ENTR & DG ENV 2003) regarding the total direct testing needs and costs for the chemical industry as a whole. Thus, the aims of the study are to (i) estimate the testing needs and costs incurred by REACH, and (ii) analyse the potential impact of the potential use of (Q)SARs, grouping and read-across.

Our estimates are based on:

1. The draft revised Business Impact Study by RPA (July 2003) based on the REACH system as described in the REACH Consultation Document.
2. The application of (Q)SARs and similar approaches as applied in the USA and Canada, in the interests of industry (time- and cost-effectiveness) and animal welfare. As stated above, it is envisaged that current approaches can be further refined before the actual implementation of the future REACH legislation.
3. Our expert opinion (the interpretation by ECB and ECVAM experts of the testing strategy and adaptation rules as described in the draft testing annexes (V-VIII) and in the adaptation annex (IX) of the REACH Consultation Document) based on practical experiences in risk assessment of chemicals over more than 10 years.
4. A detailed analysis of current regulatory obligations, i.e. only the testing needs and costs incurred by the proposed REACH system in addition to current obligations and voluntary initiatives are included. In other words, current regulatory obligations are excluded from the estimates provided in this report.
5. Cost savings for industry through the application of future *in vitro* methods have not been considered in this study.

In addition to the present study, JRC has been requested by DG ENTR to prepare estimates of the impact of implementation of the proposed REACH legislation on the testing needs and costs for the textile sector. The estimated testing needs and costs for the textile sector are presented in another report (Molander 2003).

2. METHOD

A stepwise procedure has been used for estimating the total testing needs and costs of implementing REACH as described in the Consultation Document (DG ENV and DG ENTR 2003). The assessment of the testing needs concerns only needs directly incurred by REACH over and above to testing already required under current legislation and testing already conducted or promised to be conducted by industry as a result of voluntary initiatives. The following steps have been employed:

1. Identification/estimation of number of substances within the volume bands for testing requirements
2. Identification of existing data coverage
3. Estimation of likely data coverage for non-HPVC
4. Identification of data to be provided by voluntary initiatives
5. Identification of possibilities for use of estimating techniques and read-across
6. Assessment of likely acceptance of waiving or request for further testing
7. Estimation of number of tests needed for each endpoint for each tonnage band
8. Estimation of test costs

For each of the endpoints for which data are required according to Annexes V to VIII of the REACH Consultation Document and for each of the four tonnage bands, the data coverage as a result of the following aspects is then established:

- Amount of available data
- Data promised under various programmes
- Impact of (Q)SAR, grouping and read-across
- Waiving (for other reasons as, e.g., unlikely exposure)

The resulting test needs for each endpoint and tonnage band is then estimated as 100% minus the estimated data coverage established through the above four aspects. It is assumed that there will be one test package per substance available. This assumption is based on the fact that the legislation will strongly encourage and promote sharing of test data between companies and that it provides the necessary tools for this. Therefore, duplicate testing is not assumed to take place and, if it happens, it will be the result of a voluntary initiative by industry and not a result of implementing REACH. Thus, it is anticipated that repeated registrations, if they occur, do not influence the amount of testing that will be required and conducted. However, duplicate testing cannot be excluded as an indirect effect of implementing the proposed REACH system. Therefore, the possible impact of duplicate testing on the testing costs is evaluated in the discussion section.

The various steps that have been evaluated in order to establish the data coverage for each of the endpoints are described in detail below.

2.1 Identification/estimation of number of substances

A precise estimate of the number of substances that will have to be registered with full data sets is of course crucial for a reliable estimate of the testing needs and costs.

The current legislation requires that new substances be notified together with certain information on the intrinsic properties depending on expected tonnage to be manufactured. The REACH Consultation Document requires less data to be supplied per tonnage level compared with today's requirements on data for new substances, meaning that REACH will not require additional testing for new substances, but rather the opposite. Thus, REACH will reduce testing needs and costs for new substances. Although this will reduce the overall costs of REACH, it is assumed that this reduction will be of minor importance and, thus, this has not been included in the estimates.

The phase-in substances as described in the REACH Consultation Document are substances that over the 10 years preceding the entry into force of the REACH legislation meets at least one of the following criteria:

(a) it was manufactured in or imported into the community in quantities of 1 tonne or more by the manufacturer or importer and is listed in EINECS,
(b) it was manufactured in the Community but not placed on the market in quantities of 1 tonne or more by the manufacturer or importer,
(c) it was placed on the market [...] but not meeting the definition of a polymer in Directive 92/32.

The substances under (a) are the existing substances including intermediates that were reported by industry as being placed on the market between 1971 and 1981 (EINECS substances) and, therefore, currently some of them might not be produced and marketed. This group would also include the type 4[1] (isolated, marketed) intermediates, and it could also include some type 3 (isolated, transported) intermediates depending on how the "market" requirement is interpreted. The substances under (b) would probably include the type 1 (non-isolated), type 2 (isolated, on site) and, depending on definition, type 3 (isolated, transported) intermediates, of which some substances could be new substances (i.e. not in EINECS), but it could also contain some substances only manufactured for export. It is assumed that in practice only a few new substances are included in (b). The substances under (c) are the so-called "no-longer polymers" consisting of at least 767 substances (EC 1999), which do not meet the current definition of a polymer, but which were not registered in EINECS. No information on the production quantities is available. Thus, among the phase-in substances only the existing substances and the no-longer polymers are of relevance for the current evaluation.

Additionally to the existing substances, the REACH consultation document also requires that isolated intermediates transported (type 3 intermediates) in quantities of more than 1000 tonnes/year be registered with a minimum data package as well as non-registered monomers and other substances constituting > 2% in polymers.

Information on the numbers of existing substances is available from the IUCLID database, as substances manufactured in volumes > 10 tonnes/year in the years 1991-1994 had to be re

[1] Definitions of the various types of intermediates are given in DG JRC (2003).

ported to the Commission no later than 1998 (cf. Council Regulation (EEC) No 793/93). Not all existing substances are necessarily included in IUCLID, as some EINECS substances that were not on the market in 1991-1994 may have been introduced again at a later stage. However, it is assumed that this would only pertain to very few substances. The number of substances manufactured in 1-10 tonnes/year have been estimated by subtracting the number of existing substances manufactured in volumes > 10 tonnes/year and the number of new substances manufactured in volumes > 1 tonne/year (~2500 substances according to ECB) from 30000 substances requiring registration according to the White Paper (EC 2001).

The substances in IUCLID include also intermediates that are marketed (type 4 intermediates). 2099 substances in IUCLID are used solely as intermediates and most of them in quantities >10 tonnes/year. Assuming that the same fraction of substances produced in quantities of 1-10 tonnes/years are used as type 4 intermediates as of substances produced in quantities >10 tonnes/year would give an estimated total number of type 4 intermediates at 3622 used solely as intermediates. Thus, among the existing substances a total of 5721 type 4 intermediates have been estimated as being used solely as intermediates. This number corresponds well with the number of type 4 intermediates reported by DG JRC (2003) based on a survey conducted by CEFIC, where 5800 type 4 intermediates are estimated to be on the market. Furthermore, these include also new substances of which 24% are marketed intermediates corresponding to about 600 substances.

The list of no-longer polymers contains 767 substances. No information on manufactured quantity is available and many of them may even be manufactured in quantities below 1 tonne/year. However, it is voluntary to register no-longer polymers, so the list is not exhaustive. Nevertheless, considering that this number corresponds to only 0.8% of the total number of existing substances registered in EINECS, it is assumed that they will have only a minor impact on the assessment of the testing needs, and they are thus not considered further.

For isolated intermediates transported (type 3 intermediates), which are manufactured in quantities > 1000 tonnes/year, the annex V data requirements pertain. The number has been estimated by DG JRC (2003) to 1700 substances, and this number should thus be added to the number of phase-in substances manufactured in quantities of 1-10 tonnes/year. It is not clear whether some of these are already covered in the numbers extracted from IUCLID, and as they are treated separately here, this might overestimate the testing needs. Finally, it is assumed that monomers and other substances used in polymers in quantities > 2% have already been registered (RPA 2003).

The following numbers of substances were found and are thus used as the basis for the estimates of testing needs:

Table 1. Numbers of phase-in substances

Tonnage per manufacturer/importer	**Number of substances**	**Source**
> 1000 tonnes/year (incl. type 4 intermediates)	2704	IUCLID
100 – 1000 tonnes/year (incl. type 4 interm.)	2461	IUCLID
10 – 100 tonnes/year (incl. type 4 interm.)	4977	IUCLID
1 – 10 tonnes/year (incl. type 4 interm.)	17500	From EC (2001)
Intermediates type 3, > 1000 tonnes/year	1700	DG JRC (2003)
Non-registered monomers and substances in polymers	0	RPA (2003)
Total number of phase-in substances	*29342*	

RPA & Statistics Sweden (2002) also estimated the number of phase-in substances and found more or less the same numbers for substances produced in quantities > 10 tonnes/year, but they estimated the number of substances produced in quantities of 1 – 10 tonnes/year to be 20000.

2.2 Identification of existing data coverage for HPVCs

In 1999, ECB carried out an analysis of the data available in IUCLID for HPVCs (Allanou et al. 1999) indicating coverage of 20 – 80 % for most endpoints. The Business Impact Study (RPA & Statistics Sweden 2002) concluded based on the answers provided by industry to their questionnaire that in practice more data might be available than reported under the Existing Substances Regulation. This conclusion fits with the experience obtained under implementation of this regulation, which shows that for many priority substances in reality few tests had to be performed to fulfil the base-set requirement. It is also a general experience with data collection that additional data to the ones in IUCLID can be found in easily available data sources.

In their BIS, RPA & Statistics Sweden (2002) assume that "data on physicochemical properties already exist for all existing substances, since these data should already appear on safety data sheets". The same approach is taken here.

Recently, the US-EPA (2003) has made an analysis of the data availability and actual testing plans for endpoints covered under the U.S. HPV Challenge Program (cf. the list of endpoints in table 3). This analysis showed that the overall data availability for these substances was 57%, ranging from 47% for developmental toxicity to 75% for acute toxicity. Assuming that these data are either conducted under test methods as specified in Annex X (DG ENTR & DG ENV 2003) or similar and under GLP or that the method, quality and documentation fulfil the requirements in Annex IX, paragraph 1.1.2 (DG ENTR & DG ENV 2003), the data coverage identified by US-EPA (2003) is used directly in the current evaluation for those endpoints covered for HPVCs.

For the endpoints that are not covered by the US-EPA study, the data availability as recorded in the ECB study (Allanou et al. 1999) was used although in fact more data are available. It is assumed that the majority of these data fulfil the requirements of Annex X and GLP or Annex IX (DG ENTR & DG ENV 2003) and, thus, that they are applicable for registration purposes in the EU. The fact that much more data are probably available in practice may to some extent counterbalance the possibility that some data in IUCLID may not be of a sufficient high qual

ity and documentation. In general, no information is available on the actual validity and applicability of existing data and, thus, no further analysis has been possible.

Moreover, in IUCLID all information on 6.6 Repeated dose toxicity is merged within one table and it is thus not possible to discriminate between the three different types of tests covered under this heading. It is assumed based on our general perception from the existing chemicals review programme that for substances where test data are available, they are distributed with 85%, 20% and 5%, respectively for the 6.6.1 (28-days), 6.6.2 (90-days) and 6.6.3 (long-term) endpoints (thus assuming that for some substances more than one test is available).

Finally, some endpoints are not covered by the ECB study and, in general, the availability is then set to 0%.

2.3 Estimating likely data coverage for non-HPVC

For the non-HPVCs (produced in tonnages < 1000 tonnes/year), no centralised collection of available data is required under the current legislation.

However, RPA & Statistics Sweden (2002) conducted a survey on, a.o., availability of complete data sets for different tonnage bands among manufacturers/importers and associations. The results of their survey are given in table 2 below as percentage of substances in the different tonnage bands for which data corresponding to the current base set and level 1 and 2 are available.

Table 2. Availability of complete data sets (RPA & Statistics Sweden 2002)

Tonnage band	Base set data	Level 1 data	Level 2 data
Annex VIII (> 1000 tonnes/year)	22%	7%	5%
Annex VII (100 – 1000 tonnes/year)	22%	7%	5%
Annex VI (10 – 100 tonnes/year)	17%	3%	2%
Annex V (1 – 10 tonnes/year)	17%	3%	2%

The figures in table 2 pertain to complete data sets. However, many companies may hold data for at least some of the endpoints of a data set as also demonstrated in IUCLID, meaning that using the figures as an estimate of the availability of data for the individual endpoints is a conservative approach. Nevertheless, as no other information on data availability for specific endpoints is available, these figures are used in the further estimate of testing needs.

2.4 Identification of voluntary initiatives on providing data

Testing costs are estimated as the additional costs for industry on top of the costs of the testing they have already committed themselves to under national and international programmes. Three major programmes are taken into account in the study:

1. The testing and/or information gathering going on in the US on the HPV Challenge Program. This covers more than 2150 higher volume substances for which Screening Information Data Sets (SIDS)[2] (i.e., almost Annex VI) will be publicly available by 2004 (www.hpvchallenge.com).

[2] A description of SIDS is given in OECD (2003). Manual for Investigation of HPV Chemicals.

2. The ICCA initiative covering 1000 HPVCs (almost Annex VI) for which data will be available by 2004 (www.iccahpv.com).
3. The VCI programme delivering data for a number of acute toxicity and ecotoxicity endpoints for all substances manufactured in Germany in quantities above 1 tonne/year.

It is assumed that the US HPV and the ICCA programmes altogether cover all substances produced in quantities > 1000 tonnes/year in the EU and, thus, that data on the SIDS endpoints will become available over the next few years. Hence, no additional costs as a result of REACH are foreseen and carried over to the total costs calculation for the endpoints covered by these programmes.

To investigate the possible consequences of the VCI initiative in terms of data availability, ECB has analysed the IUCLID database for those substances that have at least one German producer. This analysis showed that 74% of the HPVCs (>1000 tonnes/year) and 55% of the LPVCs (10-1000 tonnes/year) fall into this category. As no information on substances produced in volumes below 10 tonnes/year is available in IUCLID, it is assumed that 40% of these substances are produced in Germany. The endpoints covered by the VCI initiative are shown in the table below and these are thus assumed to be or become available in the coming years[3]. This assumption is underpinned by the fact that five years after the start of this initiative, most major companies have reported that most of the data are now available[4]. Most companies also seem to have carried out the Ames test. It is assumed here that the information gathered in this programme, although in many cases probably not according to the latest guidelines and/or GLP, will be of acceptable quality to fulfil the requirements of the testing annexes.

An overview of the tests covered by these programmes is given in the table below:

Table 3. Data provided through voluntary industry programmes

Test	**US HPV & ICCA (>1000 tonnes/year)**	**VCI (>1 tonnes/year)**
6.1 Skin irritation	-	+
6.2 Eye irritation	-	+
6.4.1-3 Mutagenicity screening	+	+
6.5.1-3 Acute toxicity	+	+
6.6.1 Short-term repeated dose	+	-
6.7.1 Reprotox./Development toxicity screening	+	-
7.1.1 Short-term daphnia toxicity	+	(+)*
7.1.2 Growth inhibition algae	+	-
7.1.3 Short-term fish toxicity	+	(+)*
7.2.1.1 Ready biodegradability	+	+

*) Either short-term daphnia or fish toxicity.

In addition to these programmes there are testing and assessment programmes (in particular the PBT programmes) ongoing in some of the other OECD countries. However, since these cannot be quantified they are not taken into account in the estimations.

[3] Personal communication with Dr. Fink, VCI, 18 July, 2003
[4] Personal communication with Dr. Fink, VCI, 18 July, 2003

2.5 Identification of possibilities for use of estimating techniques and read-across

Worldwide, there is increasing usage made of (Q)SAR, grouping and read-across techniques in regulatory testing programmes for chemical safety[5] concurrent with the development and validation of such methods. Also the REACH Consultation Document (DG ENTR & DG ENV 2003) recognizes the possibility to apply both weight of evidence, (Q)SARs, grouping and read-across techniques in order to assess the hazardous properties of substances. However, especially regarding the use of (Q)SARs it is stated as a precondition that the models be validated and that sufficient documentation of the models must be available. This development is assumed to be a priority activity for the coming years in the EU and assuming a successful development, it is anticipated that these techniques will be widely applied in future under REACH in particular for substances produced in lower volumes.

Consequently, the use of weight of evidence, (Q)SARs, grouping and read-across techniques has been taken into account in the estimation of test needs. The following sources were used as background for estimating how much the different data requirements potentially could be covered by these techniques:

1. The analysis on the U.S. HPV Challenge programme (US-EPA 2003) also provides information on how much use is made of SAR and QSAR techniques and read-across from similar substances in order to decide on the final testing to be performed. The analysis of the various endpoints covered for 1024 substances shows that only for 2-8 % of the total number of substances, tests are actually proposed, while (Q)SAR and read across is used to fill in 31-46 % of the data points (= 81-92 % of the missing data when available test data are excluded). The major reason for the extensive use of (Q)SAR and read-across techniques is that approximately 90% of the substances are part of categories (chemical groups). As it is assumed that the use of (Q)SARs and read-across for individual substances will be discussed and agreed among the OECD countries, including also the EU Member States, it is anticipated that these values can be used directly for the EU HPVC in the present analysis. Moreover, as the generation of data for these substances is part of the voluntary programme anyway, REACH and the use of (Q)SAR and read-across for these substances will have no direct impact on the needs for testing. However, as the current experience in the EU on the use of these techniques still lags behind the experiences in the USA, (Q)SARs are assumed to be applicable for only 70% of the substances produced in < 1000 tonnes/year where no data area available, which is 10 – 20 % lower than the use in the U.S. HPV Challenge Program.
2. For other endpoints not covered by the US-EPA analysis, evaluations made by the Danish EPA (2003) on quality of (Q)SARs for different endpoints have been used. Depending on the score given (good, fair, poor) it is assumed that a certain percentage (60%, 30%, 0%) of the tests needs can be covered by QSARs. When different scores are given for an endpoint, the average value has been used.

The use of read-across techniques is also increasing; however, still at an emerging level. In the UK, pre-notification enquiries regarding notifications of new substances now proposes read-across for some toxicological endpoints for more than 30% of the substances, and in recent years more than 10% of the actual notifications used read-across techniques for some of the toxicological endpoints based on a strategy developed by the UK Health and Safety Ex

[5] Ref to OECD special session on QSARs, November 2002.

ecutive (Hanway 2002). Also for environmental endpoints, a strategy for use of read-across data has been developed (Peter et al. 2003). However, it has not been possible to assess the potential impact of such techniques on the testing needs in the current study.

It is stated in annex IX of the REACH Consultation Document that (Q)SARs may be used to predict the existence of a certain dangerous property. However, if the model does not indicate a certain dangerous property, the relevant test shall nevertheless be carried out at the appropriate tonnage level to confirm the negative result. On the other hand, such a confirmation may be waived, if the result is derived from a validated model, if the result is adequate for the purpose of classification & labelling and risk assessment, and if adequate and reliable documentation of the method is provided. Thus, the future use of weight of evidence, (Q)SARs, grouping and read-across techniques under REACH will depend on both the scientific development of methodologies and on the political acceptability among the Member States. As the use will have a major influence on the needs for further testing, an uncertainty analysis of the impact of different uses of such techniques has therefore been carried out as well (section 2.9).

2.6 Assessment of impact of waiving and RA based testing requests

In the annexes on data requirements (Annexes V – VIII) and in the annex on rules for adaptation (Annex IX) of the REACH Consultation Document (DG ENTR & DG ENV 2003), a relatively complex system of rules has been built up. The practical implementation of these rules, in case the proposed system be adopted, and their impact on the number of tests that will be required in future is difficult to evaluate in their entirety. However, on the basis of experiences with the administration of the existing substances regulation (ESR) and the notification of new substances, reasonable assumptions have been made on the use of many of the proposed rules. As the practical decision on the need for a specific test will often depend on a combination of more than one of the rules, it has been necessary to introduce a number of generalisations in the assumptions. A justification for the various assumptions is given below:

- In practice not all substances can be tested due to methodological difficulties. It is stated in section 2 of Annex IX that testing may be omitted, if it is technically not possible to conduct the study. Substances that are petroleum and coal based substances, inorganic compounds (incl. salts) or of unknown or variable composition, complex reaction products or biological material are typical examples of such substances that cannot be tested for at least some of the endpoints. About 42% of the HPVCs in IUCLID belong to these classes (Allanou et al. 1999). Assuming that this percentage to some extent is representative for substances manufactured in lower volumes as well, but on the other hand that some of these substances can be tested anyway, a best guess would be that on average 20% of the substances lacking data cannot be tested due to methodological constraints. These 20% include also the about 650 petroleum fractions that are already classified as carcinogenic and consequently do not need further testing.
- 6.1 Skin irritation or corrosion: Adaptation of the test requirement is possible due to physicochemical and toxicological properties. It is assumed that the influence of physicochemical properties is included in the (Q)SAR and read-across evaluation, while the influence of toxicological properties has not been considered.
- 6.2 Eye irritation: As for 6.1 Skin irritation or corrosion.
- 6.3 Skin sensitisation: As for 6.1 Skin irritation or corrosion.

- 6.4 Mutagenicity: Two *in vitro* mutagenicity screening tests are required already at Annex V level and a third *in vitro* screening test at the Annex VI level, unless data from an *in vivo* mutagenicity study (6.4.4) are available. In case of a positive result in any of the screening tests, further mutagenicity studies shall be considered. It is assumed that this in all cases will be an *in vivo* mutagenicity study. Experiences from assessments of new substances show that out of 3394 notifications, 837 (~ 25%) included positive *in vitro* test results, which would require further testing under REACH. Experiences from existing substances (ESR and OECD) show that out of 78 substances, 34 (~ 45%) included positive *in vitro* test results (HSE 2003). As the ESR scheme through the prioritisation process is focused on potentially hazardous substances, a potential positive bias is introduced. It is, therefore, assumed that on average 30% of the *in vitro* screening studies under REACH will result in positive results requiring further *in vivo* mutagenicity studies. However, in practice the percentage may be lower, if the manufacturer or importer decides not to progress further with manufacturing and marketing such substances having problematic properties.
- 6.5 Acute toxicity: The studies need not be conducted for substances that are corrosive or flammable. However, no information on the number of such substances has been gathered and thus no impact has been considered in this analysis.
- 6.6 Repeated dose toxicity: The study does not need to be conducted at Annex VI level if relevant human exposure can be excluded. This is assumed to be the case for highly controlled substances possibly comprising 10% of substances at this tonnage band (10 – 100 tonnes/year). At a production quantity of > 100 tonnes/year, the 6.6.1 Short-term repeated dose toxicity study has to be conducted (unless a longer-term study is available or proposed) or the 6.6.2 Sub-chronic toxicity study may be proposed instead when there are indications of concern. The distribution between these two tests is assumed to be 75% of 6.6.1 and 25% of 6.6.2. For substances produced in quantities > 1000 tonnes/year the 6.6.2 test is again assumed to be required for 25% of the substances and in addition that the 6.6.3 Long-term repeated toxicity study may be proposed or required for 10% of the substances. The latter study would probably be combined with a 6.9 Carcinogenicity study (cf. below).
- 6.7 Reproductive toxicity: The 6.7.1 Development toxicity screening study does not need to be conducted at a production quantity of > 10 tonnes/year, if relevant human exposure can be excluded. This is assumed to be the case for highly controlled substances comprising 10% of substances. In case of a positive result in the 6.7.1 test, also a 6.7.2 Development toxicity study shall be conducted (tentatively assumed for 15% of substances based on findings of Reuter et al. (2003), although depending on whether the manufacturer or importer will withdraw such substances from the market). Depending on a positive result in the 6.6 Repeated dose toxicity studies (assumed for 15% of substances), the 6.7.3 Two-generation reproductive toxicity study shall be proposed. At a production quantity of > 100 tonnes/year, the 6.7.2 Development toxicity study will normally have to be conducted (assumed for 90% of substances), and the 6.7.3 Two-generation reproductive toxicity study may be required depending on the outcome of 6.6 Repeated dose toxicity studies (assumed for 15% of substances). Both of the tests normally have to be conducted at a production quantity of > 1000 tonnes/year (assumed for 80% of these substances taking into account that about 17% of the HPVCs are petroleum compounds already classified as carcinogic and consequently no further reproductive toxicity testing is needed). As the outcome of the development toxicity screening study (6.7.1) and the repeated dose toxicity studies (6.6) are decisive for whether or not the developmental toxic

ity study (6.7.2) and/or the two-generation toxicity study is needed, and as no specific information has been collected to support the assumption that 15% of these tests are positive, the impact of varying the assumption on number of positives has been included in the uncertainty analysis (section 2.9).

- 6.9 Carcinogenicity: A study may be proposed or required for substances that are mutagenic category 3 (assumed ~ 30% although depending on whether the manufacturer or importer will withdraw such substances from the market) or causing concern based on a repeated dose toxicity study and if it has a widespread use or there is evidence of frequent or long-term human exposure. This is assumed to be the case for 10% of substances.
- 7.1.4 Activated sludge respiration inhibition testing: Additional to the general waiving due to test difficulties, it is assumed that 20% of substances are waived due to ready biodegradability demonstrated in tests with concentrations in a realistic range.
- 7.1.5 Long-term toxicity testing on *Daphnia* & 7.1.6 Long-term toxicity testing on fish: It is assumed that based on results of risk assessments, long-term toxicity testing is required for 5% of substances produced in quantities < 100 tonnes/year and for 10% of substances produced in quantities > 100 tonnes/year.
- 7.2.1.1 Ready biodegradability: It is assumed that 10% of the substances on EINECS are inorganic based on information that 5% of 80000 substances having a molecular formula are inorganics and that probably much more of the 20000 substances not having a molecular formula are inorganics (Danish EPA 2003).
- 7.2.1.2-4 Biodegradation simulation tests for surface water, soil and sediment: It is assumed that such tests are required for 10% of all substances based on the outcome of risk assessments.
- 7.2.1.5 Confirmatory testing of biodegradation: It is assumed that such tests are required for 1% of all substances based on the outcome of risk assessments.
- 7.2.3 Identification of degradation products: It is assumed that such tests are required for 1% of all substances based on the outcome of risk assessments.
- 7.3.1 Adsorption/desorption screening study: 60% of organic substances have a log Pow < 3 (Danish EPA 2003) and thus a low potential for sorption to particles.
- 7.3.2 Accumulation in one aquatic species: 60% of organic substances have a log Pow < 3 (Danish EPA 2003) and thus a low potential for bioaccumulation in aquatic species.
- 7.3.3 Further adsorption/desorption studies: It is assumed that such tests are required for 1% of all substances based on the outcome of risk assessments.
- 7.3.4 Further environmental fate and behaviour studies: It is assumed that such tests are required for 1% of all substances based on the outcome of risk assessments.
- 7.4.1-3 Short-term toxicity to earthworms, soil micro-organisms and plants: It is assumed that these tests may be required for 50% of substances with a log Pow > 4 (which according to the Danish EPA (2003) is about 25% of all organics).
- 7.4.4-6 Long-term toxicity to earthworms, soil micro-organisms and plants: It is assumed that these tests can be waived for 95% of substances.
- 7.5 Long-term toxicity to sediment organisms: It is assumed that these tests can be waived for 90% of substances.
- 7.6 Long-term or reproductive toxicity to birds: It is assumed that exposure of birds is likely for 1% or substances.
- 9. Methods of detection and analysis: It is assumed that description of these methods will be requested for 10% of substances.

The above assumptions have been applied in the estimation for each of the data endpoints in each of the four tonnage bands for the remaining testing needs following the assessment of number of available (test) data, number of promised submissions and the use of (Q)SAR, grouping and read-across.

2.7 Estimating number of tests needed for each data requirement

When the percentages of substances for which the data needs will be filled in by QSARs or most likely will be waived are known for each endpoint, the remaining percentage per tonnage category is multiplied by the number of substances for each tonnage band. This results in the total number of tests that are expected to be carried out.

For some data points, a choice is required about which of different test possibilities that should be conducted. These possibilities are discussed below together with a proposed distribution of the tests, which is mainly based on general experiences from implementing the ESR. The proposed distribution of tests is in all cases greater than 100%, which allows for situations where more than one of the possible tests is conducted.

- 6.5 Acute toxicity: Data on acute toxicity are required at production volumes of > 10 tonnes/year. Three different tests are available: 6.5.1 Oral toxicity, 6.5.2 Inhalation toxicity and 6.5.3 Dermal toxicity. Normally, oral toxicity shall be determined together with toxicity through one of the other two routes; inhalation or dermal. As the current development of testing strategies (EC 2003) points towards increasing use of the inhalation test as the second acute toxicity test, it is tentatively assumed that the distribution of tests in future will be 90%, 50% and 40%, respectively.
- 7.2 Degradation simulation tests: These studies may be required for substances produced in volumes of 10 – 100 tonnes/year depending on the outcome of risk assessments, and shall be proposed for substances produced in volumes of > 100 tonnes/year. One or more of three different tests may be proposed/required: 7.2.1.2 Surface water simulation test, 7.2.1.3 Soil simulation test, and 7.2.1.4 Sediment simulation test. The distribution between these tests is tentatively assumed to be 80%, 15% and 15%, respectively.
- 7.4 Terrestrial ecotoxicity tests: Short-term ecotoxicity tests may be required for substances produced in volumes of > 100 tonnes/year. The following tests are available: 7.4.1 Short-term toxicity to earthworms, 7.4.2 Effects on soil micro-organisms, and 7.4.3 Short-term toxicity to plants. Long-term ecotoxicity tests may be required for substances produced in volumes > 1000 tonnes/year with the following tests available: 7.4.4 Long-term toxicity to earthworms, 7.4.5 Long-term toxicity to soil invertebrates, and 7.4.6 Long-term toxicity to plants. The following distribution of tests is anticipated: 45%, 20% and 45% both for the three short-term and the three long-term tests, respectively.

2.8 Estimating test costs

The testing costs have been estimated from the calculated number of tests required for each endpoint in each tonnage band multiplied with a standard cost of each of the tests. In the updated Business Impact Study by RPA (2003), details of test costs based on a new survey are included in their Annex 1. Whenever possible, these test costs have been used directly in the current cost estimate. However, for some tests the information provided by RPA is not applicable and instead other sources have been used. This is the case for the three *in vitro* tests for mutagenicity (6.4.1 *In vitro* gene mutation study in bacteria, 6.4.2 *In vitro* cytogenicity study in mammalian cells, and 6.4.3 *In vitro* gene mutation study in mammalian cells), where test

costs provided by SafePharm Laboratories (2003) have been used, identification of degradation products (7.2.3 Identification of degradation products), where the cost has been guessed, and cost of development of analytical methods, where prices have been reported as an average of European contract institutes costs (2500 – 4000 EURO). Furthermore, the costs of the long-term ecotoxicity tests with terrestrial and sediment organisms (76000 EURO per test) seem much to high, but as they have no decisive influence on the final cost estimate, no efforts have been made on providing more precise costs. Note that the cost estimate has been based on current test prices and, thus, no attempts have been made to take into account inflation or to discount future costs.

The average testing costs for a substance produced in each of the four tonnage bands has furthermore been estimated by dividing the total testing costs for each of the four annexes with the estimated number of substances. Additionally, the average testing cost per tonne of a substance has been estimated as well under the assumption that the average quantity produced is 3, 30, 300 and 3000 tonnes/year for the respective tonnage bands and that the costs are distributed equally over 10 years.

2.9 Uncertainty analysis

Inevitably, the estimation of future testing needs and costs under the proposed REACH system is based on numerous assumptions as described in the above sections. Naturally, the validity of the various assumptions differs, and also the consequences of uncertainties in the assumptions on the testing needs and costs differ. It is assumed that the assumptions relating to the numbers of phase-in substances, the existing data coverage, the impact of voluntary initiatives and some of the waiving/requiring of additional tests as a result of the outcome of risk assessments are relatively well-founded. Moreover, it is anticipated that these factors more or less compensate for each other and altogether, they will thus have a relatively minor impact on the estimated testing needs and costs. Thus, the main factor impacting the estimation results is then some of the waiving/requiring of additional tests as a result of the outcome of risk assessments and the acceptance of alternative approaches to data generation (weight of evidence, (Q)SARs, grouping and read-across techniques).

The uncertainty analysis comprises two boundary scenarios – a minimum test needs scenario and a maximum test needs scenario, which are described below.

Minimum test needs scenario

The minimum test needs scenario appears when either waiving of specific tests or extensive use of (Q)SARs, grouping and read-across techniques is employed.

The tests for reproductive toxicity are among the most costly tests and as the need for the developmental toxicity study (6.7.2) and/or the two-generation reproductive toxicity study (6.7.3) depends on the outcome of other studies that is difficult to predict, the impact of assuming that these tests need to be conducted for only 10% of the substances for which no data are available, has been evaluated.

Regarding (Q)SARs, grouping and read-across, it is assumed that the approach already used under the U.S. HPV Challenge Program is accepted also in the EU, meaning that the same acceptance probability for the endpoints covered is used for non-HPVCs as for the HPVCs. Furthermore, for endpoints not covered by the U.S. HPV Challenge Program, but where esti

mation techniques are already under development and are giving scores as either good, fair or poor, it is assumed that 80%, 40% and 10%, respectively, of the test needs can be covered by QSARs as a result of intensive research in the years to come. Table 4 shows the anticipated use of (Q)SARs, grouping and read-across techniques as the percentage of substances for which no data are available where estimation techniques may be used to deliver the data in stead of testing.

Table 4. Optimal use of (Q)SARs, grouping and read-across techniques

Endpoint	**Acceptance**	**Source**
6.1 + 6.1.1 Skin irritation/corrosion	80%	DK-EPA(1)
6.2 + 6.2.1 Eye irritation	40%	DK-EPA
6.3 Skin sensitisation	60%	DK-EPA
6.4.1-3 *In vivo* mutagenicity screening tests	91%	US-EPA
6.5.1-3 Acute toxicity	92%	US-EPA
6.6.1 Short-term repeated dose	92%	US-EPA
6.6.2 Sub-chronic toxicity	40%	DK-EPA
6.6.3 Long-term repeated toxicity	40%	DK-EPA
6.7.1 Development toxicity screening	86%	US-EPA
6.7.2 Development toxicity study	25%	DK-EPA
6.7.3 Two-generation reproduction toxicity	10%	DK-EPA
7.1.1 Short-term *Daphnia* toxicity	83%	US-EPA
7.1.2 Growth inhibition study on algae	85%	US-EPA
7.1.3 Short-term fish toxicity	85%	US-EPA
7.1.5 Long-term *Daphnia* toxicity	45%	DK-EPA
7.1.6 Long-term fish toxicity	45%	DK-EPA
7.2.1.1 Ready biodegradability	82%	US-EPA
7.2.2.1 Hydrolysis	45%	DK-EPA
7.3.1 Adsorption/desorption	80%	DK-EPA
7.3.2 Accumulation in aquatic species	80%	DK-EPA

(1) Our interpretation of information supplied by DK-EPA (2003).

Maximum test needs scenario

In the maximum test needs scenario it is assumed that the developmental toxicity study (6.7.2) and/or the two-generation reproductive toxicity study (6.7.3) need to be conducted for 25% of the substances for which no data are available.

Furthermore, only limited use of (Q)SARs, grouping and read-across techniques is assumed. This corresponds to the approach used by RPA (2003) in their draft update of their BIA, where "some acceptance of QSAR positives" is assumed. RPA estimates the QSAR Regulatory Acceptance Probability by multiplying a QSAR Performance Probability, a QSAR Domain Probability and an Exposure Probability. The first two factors are related to the Danish EPA judgement on the applicability of QSARs for various endpoints (cf. section 2.5) and the latter is related to the tonnage bands, i.e. the regulatory acceptability of the use of a certain QSAR is assumed to depend on the manufactured volume of a substance. Using the RPA approach, the acceptance probability in table 5 is calculated.

Table 5. Estimated QSAR Regulatory Acceptance Probability (from RPA 2003)

QSAR quality	1 – 10 tonnes/year	10 – 100 tonnes/year	100 – 1000 tonnes/year	> 1000 tonnes/year
Good	48%	24%	6%	3%
Fair	20%	10%	2.5%	1.25%
Poor	0.8%	0.4%	0.1%	0.05%

The estimated QSAR Regulatory Acceptance Probabilities are then used for estimating the likely use of QSAR in stead of testing for each endpoint in each tonnage band based on the judgement of the reliability of the available QSARs as provided by the Danish EPA (2003).

3. RESULTS

The estimations of the testing needs and costs for the three scenarios have been done in three spreadsheets, which are attached to this document. All the details of the estimations may be found there, while only an overview of the results is presented below in the current document.

3.1 Estimated number of tests needed

The estimated numbers of tests for each endpoint under each of the three scenarios is shown in the Annex. In total 29342 phase-in substances and intermediates are included in the assessment. The endpoints for which most tests are needed are shown in table 6 below. Only endpoints for which testing is required for more than 6% of the substances in the average scenario are shown with the endpoints requiring most tests in the average scenario shown first.

Table 6. Estimated testing needs (% of total number of substances)

Endpoint	Minimum	Average	Maximum
6.3 Skin sensitisation	7486 (25.5)	10293 (35.1)	13728 (46.8)
6.2 Eye irritation (incl. *in vivo*)	5923 (20.1)	6910 (23.5)	8182 (27.9)
6.4.4 *In vivo* mutagenicity study	6580 (22.4)	6580 (22.4)	6580 (22.4)
7.1.2 Growth inhibition algae	2638 (9.0)	5277 (18.0)	11466 (39.1)
7.1.4 Active sludge respiration test	4616 (15.7)	4616 (15.7)	4616 (15.7)
7.1.1 Short-term *Daphnia* toxicity	2321 (7.9)	4096 (14.0)	8798 (30.0)
6.1 Skin irritation/corrosion (incl. *in vivo*)	1974 (6.7)	3949 (13.4)	5817 (19.9)
7.2.2.1 Hydrolysis	2691 (9.2)	3425 (11.7)	4518 (15.4)
6.4.1 Gene mutation study in bacteria	875 (3.0)	2916 (9.9)	6424 (21.9)
6.4.2 Cytogenicity study in mammalian cells	875 (3.0)	2916 (9.9)	6424 (21.9)
6.7.2 Development toxicity study	2408 (8.2)	2893 (9.9)	3711 (12.6)
7.2.1.1 Ready biodegradability test	1574 (5.4)	2624 (8.9)	5752 (19.6)
6.7.3 Two-generation reproduction toxicity	1665 (5.7)	2135 (7.3)	2699 (9.2)

A large number of the tests that are needed according to the estimates, require testing on vertebrate animals. In particular, this pertains to the *in vivo* mutagenicity study (6.4.4), the development toxicity study (6.7.2) and the two-generation reproduction toxicity study (6.7.3), but also some of the estimated needs for eye and skin irritation studies will have to be *in vivo* studies.

3.2 Estimated testing costs

The estimated testing costs for each of the four tonnage bands and in total are shown in table 7 for the minimum testing needs scenario, the average testing needs scenario and the maximum testing needs scenario.

Table 7. Estimated testing costs (Million EURO)

Scenario	1 – 10 tonnes/year	10 – 100 tonnes/year	100 – 1000 tonnes/year	> 1000 tonnes/year	Total
Minimum test needs	164	201	315	499	1180
Average test needs	233	364	401	564	1561
Maximum test needs	316	755	600	752	2423

The distribution of the testing costs on the different endpoints is shown in table 8 with the most expensive endpoints shown first in the table. Only endpoints with total costs of more than 20 Million EURO in the average scenario are shown.

Table 8. Estimated testing costs for most costly endpoints (Million EURO)

Endpoint	**Minimum**	**Average**	**Maximum**
6.7.2 Development toxicity study	396	476	611
6.7.3 Two-generation reproduction toxicity	293	376	475
6.4.4 *In vivo* mutagenicity study	129	129	129
6.6.2 Sub-chronic toxicity	76	111	210
6.6.3 Long-term repeated dose toxicity study (incl. 6.9 Carcinogenicity study)	44	52	73
6.6.1 Short-term repeated dose toxicity study	13	49	189
6.4.2 Cytogenicity study in mammalian cells	16	52	116
6.3 Skin sensitisation	29	40	54
7.2.1.1 Ready biodegradability test	19	32	71
7.3.2 Accumulation	14	28	67
7.1.2 Growth inhibition algae	13	26	57
6.7.1 Development toxicity screening	12	26	101
7.2.2.1 Hydrolysis	16	21	28

The testing costs per substance undergoing testing in each of the tonnage bands are presented in table 9 below.

Table 9. Estimated average testing costs per substance (kEURO)

Scenario	**1 – 10 tonnes/year**	**10 – 100 tonnes/year**	**100 – 1000 tonnes/year**	**> 1000 tonnes/year**
Minimum test needs	8.6	40.5	128	185
Average test needs	12.1	73.1	163	208
Maximum test needs	16.4	152	244	278

The estimated testing costs per tonne of an average substance are estimated assuming the production of 3, 30, 300 and 3000 tonnes/year, respectively, and that the costs are distributed equally over 10 years.

Table 10. Estimated testing costs over 10 years per tonne of an average substance (EURO)

Scenario	**1 – 10 tonnes/year**	**10 – 100 tonnes/year**	**100 – 1000 tonnes/year**	**> 1000 tonnes/year**
Minimum test needs	285	135	43	6
Average test needs	404	244	54	7
Maximum test needs	548	506	81	9

4. DISCUSSION

The estimated numbers of tests needed for each data endpoint is a function of the basic information requirements for each tonnage band, the number of already available tests, the number

of tests already promised, the possibilities for estimating the result by use of (Q)SARs, grouping and read-across, and the possibilities for waiving.

The basic information requirements for a substance depending on the produced quantity are described as a testing strategy in Annexes V – VIII and possibilities for adaptation of the general rules are described in Annex IX of the REACH Consultation Document (DG ENTR & DG ENV 2003). It is worthwhile mentioning that the testing requirements are focused on specific tests and not on availability of general information about the various endpoints. This means that, according to our interpretation of the testing annexes, even though some information on a certain endpoint may be available, this is not sufficient if the prescribed test is not available. However, the practical implementation of the testing strategy may be more lenient and in this case, the current estimates may be conservative.

The lack of test data on not only the HPVCs, but even more the LPVCs, has been recognised for now more than two decades. A result of this is a number of voluntary programmes, where industry generates data on mainly the so-called SIDS endpoints, i.e. the endpoints that are required under the OECD programme on HPVCs (OECD 2003). However, despite the ongoing programmes on submission of data, there is still a long way to go before sufficient information becomes available for assessing the safe use of all chemicals and this has been one of the main incentives for developing the REACH system.

One option for providing sufficient data without conducting a large number of laboratory tests is to use estimation techniques as (Q)SARs, grouping and read-across. The use of such methodologies is encouraged in the REACH Consultation Document (Annex IX) provided that adequate and reliable documentation is submitted and, for (Q)SARs, that the applied model has been validated. The current analysis of the possible use of such techniques based on the current practice in the US-EPA shows that they may have a large impact of the number of tests required for some of the endpoints. The minimum and maximum use of (Q)SARs results in 3-4 times higher, respectively lower, numbers of tests required for the endpoints short-term repeated dose toxicity study (6.6.1), acute toxicity (6.5.1-3) and mutagenicity screening (6.4.1-3), and in about 2-3 times higher, respectively lower, numbers required for development toxicity screening (6.7.1), short-term aquatic toxicity tests (7.1.1-3), accumulation (7.3.2), adsorption/desorption (7.3.1), and ready biodegradability test (7.2.1.1).

The possibilities for waiving a specific test or requesting a specific test are difficult to assess, as this in the end to a large extent will depend on the outcome of the safety assessment, which is unpredictable on a generic level. However, the current experiences from administering the existing and new substances review programmes for more than 10 years have been taken into account, as it may to a certain extent be possible to extrapolate to all of the phase-in substances. An assessment has been made for each individual endpoint for each of the up to four tonnage bands for which the data is needed. The assumptions are described and discussed at length in section 2.6. Care has been taken not to overestimate the possible use, as the substances covered in the existing substances programme are selected through a comprehensive prioritisation process and, thus, are not representative. Neither are the new substances necessarily representative for phase-in substances.

By taking all of the above assumptions into account, the numbers of tests needed for each of the endpoints are estimated. It is estimated that the 6.3 skin sensitisation test needs to be con

ducted for 35% of the total number of phase-in substances followed by 6.4.4 further mutagenicity tests for 22%, 6.2 eye irritation test for 18%, 7.1.2 algae growth inhibition tests for 18% and 7.1.4 active sludge respiration inhibition test for 16% of the substances. Tests for all other endpoints are required for less than 15% of the total number of substances. The endpoints for which testing is needed for more than 5% of the total number of phase-in substances are shown in figure 1, while more details are given in the annex.

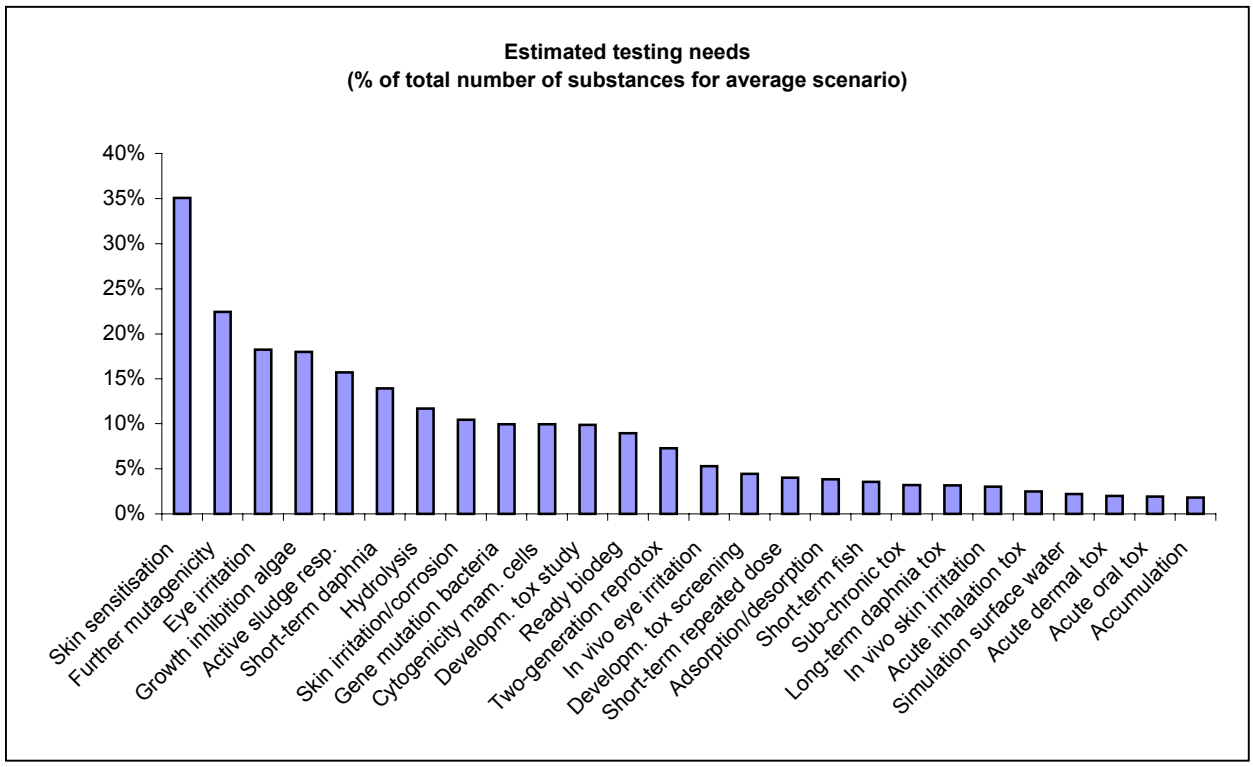

Figure 1. Estimated testing needs (% of total number of substances) for endpoints for which tests are required for more than 2% of all substances

The transformation of numbers of specific tests needed in the various scenarios into costs provides an easily understandable and comparable measure. The test price for each of the endpoints has been obtained from mainly the draft updated RPA study, and no effort has been taken to evaluate the reliability of these test prices, even though some of them appear to be higher than normally anticipated. The direct testing costs have been estimated to be 1.6 Billion EURO for the most likely scenario (average scenario). About 86% of the estimated costs will be needed for testing for human health endpoints, while only about 14% will be needed for environmental endpoints and almost nothing for development of analytical methods. The distribution of the testing costs on the various endpoints is shown in figure 2 and more details in figures in the annex. It is estimated that 31% of the total testing costs will be used for development toxicity studies (6.7.2), 24% will be used for two-generation reproductive toxicity studies (6.7.3), and 8% will be used for *in vivo* mutagenicity studies (6.4.4). The three repeated dose toxicity studies (6.6.1-3) including the carcinogenicity study (6.9) will require in total 14% of the total testing costs.

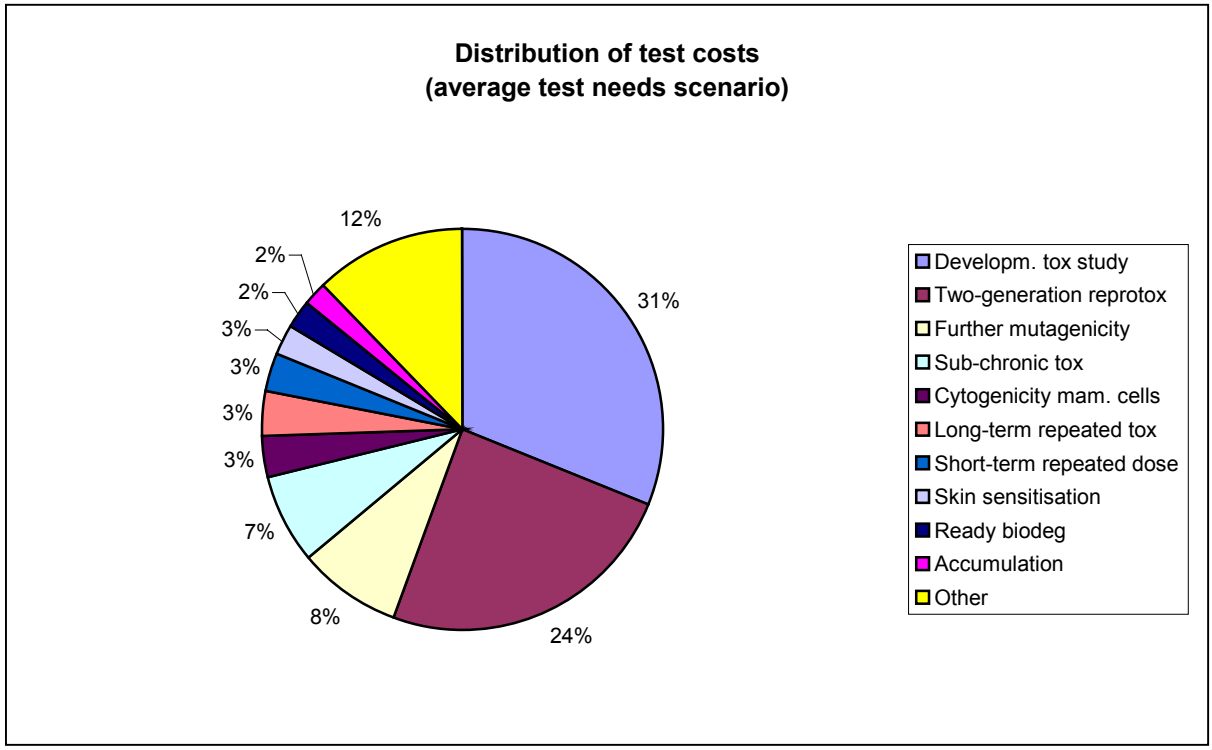

Figure 2. Distribution of estimated test costs among different endpoints in the average testing needs scenario

The uncertainty analysis on the need for two of the reproductive toxicity studies and on the use of (Q)SAR, grouping and read-across techniques for estimating data shows that, depending on the acceptability of this use, the total test costs would range from 1.2 to 2.4 Billion EURO for maximum, respectively minimum, use of these techniques. In particular for deciding on whether the developmental toxicity study (6.7.2) and/or the two-generation reproductive toxicity study (6.7.3) are needed, the outcome of the screening study for developmental toxicity (6.7.1), respectively the repeated dose toxicity studies (6.6.1-3) are decisive. The most likely scenario shows that these two studies alone cost about 850 million EURO, but that the costs may vary between about 700 million EURO and 1100 million EURO (taking into account both the possible outcome of the decisive studies and use of estimation techniques).

The scenario with the minimum use of estimation techniques uses the same assumptions regarding the use of (Q)SARs as RPA (2003) in their updated Business Impact Study. RPA estimates the total test costs to 3.4 Billion EURO (excluding costs for phase-in polymers), which is then 1.0 Billion EURO higher than the present estimate. However, using the same assumptions regarding use of (Q)SARs as RPA would result in a total test cost of 2.3 Billion EURO in comparison to our best estimate of 1.6 Billion EURO. If no (Q)SARs are used, the total testing cost would be 2.5 Billion EURO. The difference between the RPA study and our study is not easy to explain due to the somewhat different calculation techniques used. Whereas RPA calculated the average testing costs per statistical substance, we have tried to calculate precisely the number of tests that will be done for each endpoint. However, looking at Tables 4.11 and 4.12 of the draft RPA report, it seems that a major part of their cost estimate results from level 1 and level 2 testing for the higher volume substances. The average

costs per substance for level 1 and 2 are strongly determined by relatively high estimates for the percentage of substances that will undergo testing for endpoints such as reproductive toxicity (90%) and carcinogenicity (50% of the HPVCs). In addition, also very high percentages are estimated for level 2 environmental testing. Clearly, our estimations for the possibilities for waiving of testing for the higher tonnage substances based for instance on the outcome of the risk assessment or as a result of reading across from other substances are higher. We expect for instance that many of the level 2 environmental testing can be waived by referring to the outcome of the chemical safety assessment. In addition, we have included corrections for the level 2 testing requirements for those substances, which have already been classified as CMR (e.g. about 650 petroleum compounds are classified as carcinogenic, cat. 2).

The scenario with the optimal use of estimation techniques illustrates our best judgement, if the regulatory use of validated (Q)SARs for fully replacing tests is exploited. The practical implementation of such an approach would not only require that the current activities in the EU and the OECD as well as in the research environments and in industry on development, validation and adoption of (Q)SAR methodologies be intensified in the coming years, but also that this possibility is expressed more clearly in the REACH legislation than in the current REACH Consultation Document.

The total testing costs of course also depend on the degree of duplicate testing. In our estimate, we assume that this will not take place as REACH not only will encourage and promote sharing of test data, but also provides the necessary tools for this. However, in case that industry anyway conducts duplicate testing, this could be seen as an indirect effect of REACH. RPA (2003) assumes that there will be 20% repeat registrations of phase-in substances. However, this will not necessarily lead to 20% duplicate testing, as no vertebrate animal testing will have to be conducted before registration, but in stead a testing proposal will have to be submitted. It is likely that the Rapporteur Member State in case of proposed duplicate testing will react on this and request the registrants to share their data. Note that already today, some member states (e.g. Germany) have legislation in place that allows them to enforce data sharing. Thus, duplicate testing would probably only lead to marginally increased testing costs and this would not be a direct impact of REACH, but an indirect impact.

The testing requirements and thus the costs depend on the produced quantity of a substance. In the most likely scenario, the total testing costs are distributed with 15%, 23%, 26% and 36% for substances produced in quantities of 1 – 10, 10 – 100, 100 – 1000 and > 1000 tonnes/year, respectively. The claim by CEFIC that the fine and specialty chemical sectors producing chemicals in low tonnages accounting for 20% of the total chemical industry manufacture will have to bear over 80% of the direct costs of testing and administration (CEFIC 2003) cannot be supported by the present analysis.

The present analysis shows that the average testing costs per substance increases from 12000 EURO for a substance produced in a quantity of 1 – 10 tonnes/year to 208000 EURO for a substance produced in a quantity of more than 1000 tonnes/year. However, the testing costs per produced quantity of a substance are much higher for substances produced in low volumes than in high volumes with test costs distributed over 10 years decreasing from 404 EURO/tonne for a substance produced in 3 tonnes/year to only 7 EURO/tonne for a substance produced in 3000 tonnes/year.

5. CONCLUSIONS AND RECOMMENDATIONS

The present assessment of the impact of the proposed REACH system as described in the REACH Consultation Document, on the needs and costs of testing covers only the direct impact, which REACH incurs in addition to any existing obligations as a result of the current legislation and in addition to any existing voluntary initiatives regarding submission of data on, in particular, HPVCs. This means that costs of preparing the registration dossiers are not included. Note that savings on testing will lead to increased costs on preparing the dossier as justification for not conducting a test (e.g. (Q)SAR, waiving justification) needs to be substantiated.

Furthermore, the estimates are based on our understanding of how the testing strategy and adaptation rules will be implemented. The background for the estimation is information available to ECB regarding numbers of substances, availability of data, ongoing initiatives on providing data, possibilities for use of estimation techniques and read-across, and possibilities for waiving or requiring tests based on risk assessment consideration. The information is collected from various external sources as well as from the general experiences with managing the Existing Substances Regulation and the notification of new substances.

According to the estimations, the highest numbers of tests are required for the endpoints skin sensitisation (for ~ 35% (26 – 47%) of all substances), eye irritation (~ 24% (20 – 28%) of which 5% are *in vivo* tests) and the *in vivo* mutagenicity study (~ 22%). For all other endpoints, new testing is required for less that 20% of the substances.

The direct testing costs have been estimated to 1.6 Billion EURO for the most likely scenario (average scenario); however ranging from 1.2 to 2.4 Billion EURO depending on the assumptions in the uncertainty analysis. About 86% of the estimated costs will be needed for testing for human health endpoints, while only about 14% will be needed for environmental endpoints and almost nothing for development of analytical methods. It is estimated that 30% of the total testing costs will be used for development toxicity studies (6.7.2), 24% will be used for two-generation reproductive toxicity studies (6.7.3), and 8% will be used for *in vivo* mutagenicity studies (6.4.4). The three repeated dose toxicity studies (6.6.1-3) including the carcinogenicity study (6.9) will require in total 14% of the total testing costs.

The testing requirements and thus the costs depend on the produced quantity of a substance. In the most likely scenario, the total testing costs are distributed with 15%, 23%, 26% and 36% for substances produced in quantities of 1 – 10, 10 – 100, 100 – 1000 and > 1000 tonnes/year, respectively.

The present analysis shows that the average testing costs per substance increases from 12000 EURO for a substance produced in a quantity of 1 – 10 tonnes/year to 208000 EURO for a substance produced in a quantity of more than 1000 tonnes/year. However, the testing costs per produced quantity of a substance are much higher for substances produced in low volumes than in high volumes with test costs distributed over 10 years decreasing from 404 EURO/tonne for a substance produced in 3 tonnes/year to only 7 EURO/tonne for a substance produced in 3000 tonnes/year.

The potential use of (Q)SARs, grouping and read-across will have a major influence on the testing needs and costs. The estimates of the minimum and maximum use of (Q)SARs show

that up to 3-4 times higher, respectively lower, numbers of tests may be required for the various endpoints. The use of *in vitro* tests, not considered in the current study, will further reduce the use of animals in toxicity tests. The impact on the use of animals for laboratory toxicity testing will be further explored in the near future. It is therefore recommended that current activities in the EU and the OECD as well as in the research environments and in industry on development, validation and adoption of both (Q)SAR methodologies and *in vitro* tests be intensified in the coming years in order to meet the needs.

Finally, it should be emphasised that the present estimate of testing needs and costs is based on the description of the REACH system as appearing in the REACH Consultation Document of May 2003. If the further development of the legislative text and in particular the testing strategy and the adaptation rules results in major changes, it may be necessary to update the present study.

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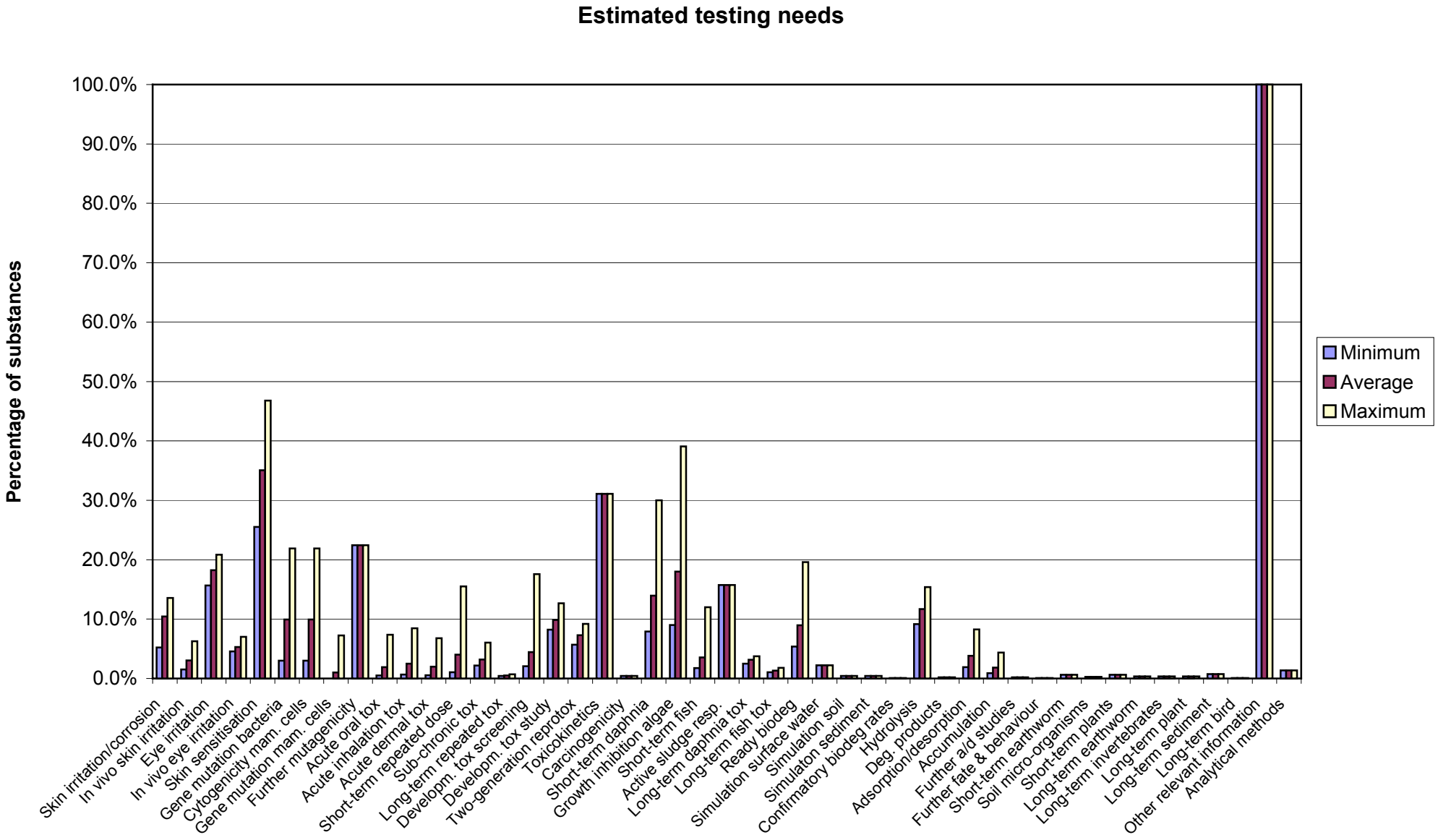
ANNEX

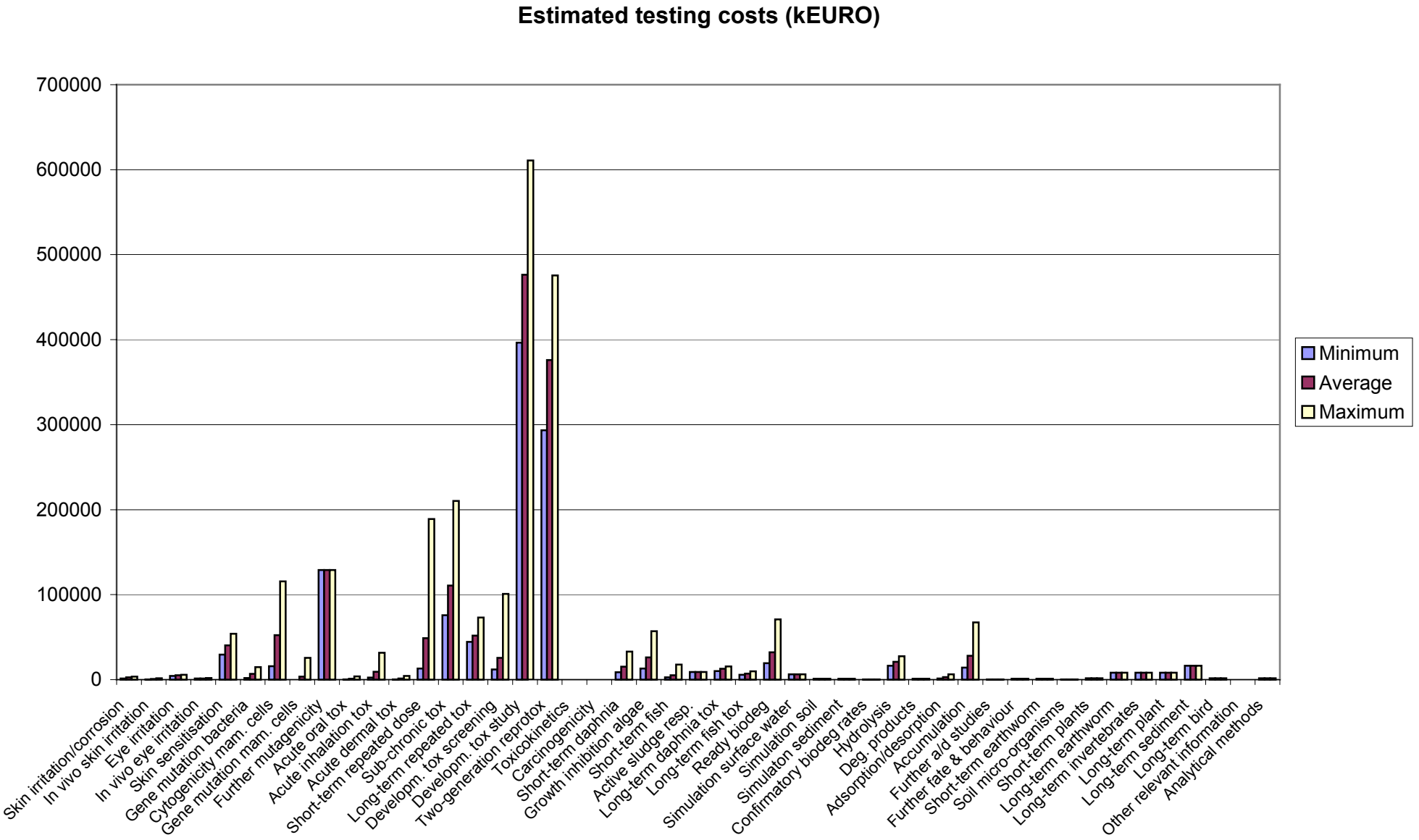
The annex contains the following three figures:

- Estimated testing needs for each endpoint in % of total number of phase-in substances for the minimum, the average and the maximum testing needs scenarios
- Estimated testing costs for conducting the estimates number of tests for each endpoint for the minimum, the average and the maximum testing needs scenarios
- Distribution of total testing costs on the different endpoints for the minimum, the average and the maximum testing needs scenarios

All calculations are available in the three spreadsheets:

- Testing needs estimate.xls
- Testing needs estimate min.xls
- Testing needs estimate max.xls


Estimated testing needs
Percentage of substances
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
Minimum
Average
Maximum
Skin irritation/corrosion
In vivo skin irritation
Eye irritation
In vivo eye irritation
Skin sensitisation
Gene mutation bacteria
Cytogenicity mam. cells
Gene mutation mam. cells
Further mutagenicity
Acute oral tox
Acute inhalation tox
Acute dermal tox
Short-term repeated dose
Sub-chronic tox
Long-term repeated tox
Developm. tox screening
Developm. tox study
Two-generation reprotox
Toxicokinetics
Carcinogenicity
Short-term daphnia
Growth inhibition algae
Short-term fish
Active sludge resp.
Long-term daphnia tox
Long-term fish tox
Ready biodeg
Simulation surface water
Simulation soil
Simulaton sediment
Confirmatory biodeg rates
Hydrolysis
Deg. products
Adsorption/desorption
Accumulation
Further a/d studies
Further fate & behaviour
Short-term earthworm
Soil micro-organisms
Short-term plants
Long-term earthworm
Long-term invertebrates
Long-term plant
Long-term sediment
Long-term bird
Other relevant information
Analytical methods


Estimated testing costs (kEURO)
700000
600000
500000
400000
300000
200000
100000
0
Minimum
Average
Maximum
Skin irritation/corrosion
In vivo skin irritation
Eye irritation
In vivo eye irritation
Skin sensitisation
Gene mutation bacteria
Cytogenicity mam. cells
Gene mutation mam. cells
Further mutagenicity
Acute oral tox
Acute inhalation tox
Acute dermal tox
Short-term repeated dose
Sub-chronic tox
Long-term repeated tox
Developm. tox screening
Developm. tox study
Two-generation reprotox
Toxicokinetics
Carcinogenicity
Short-term daphnia
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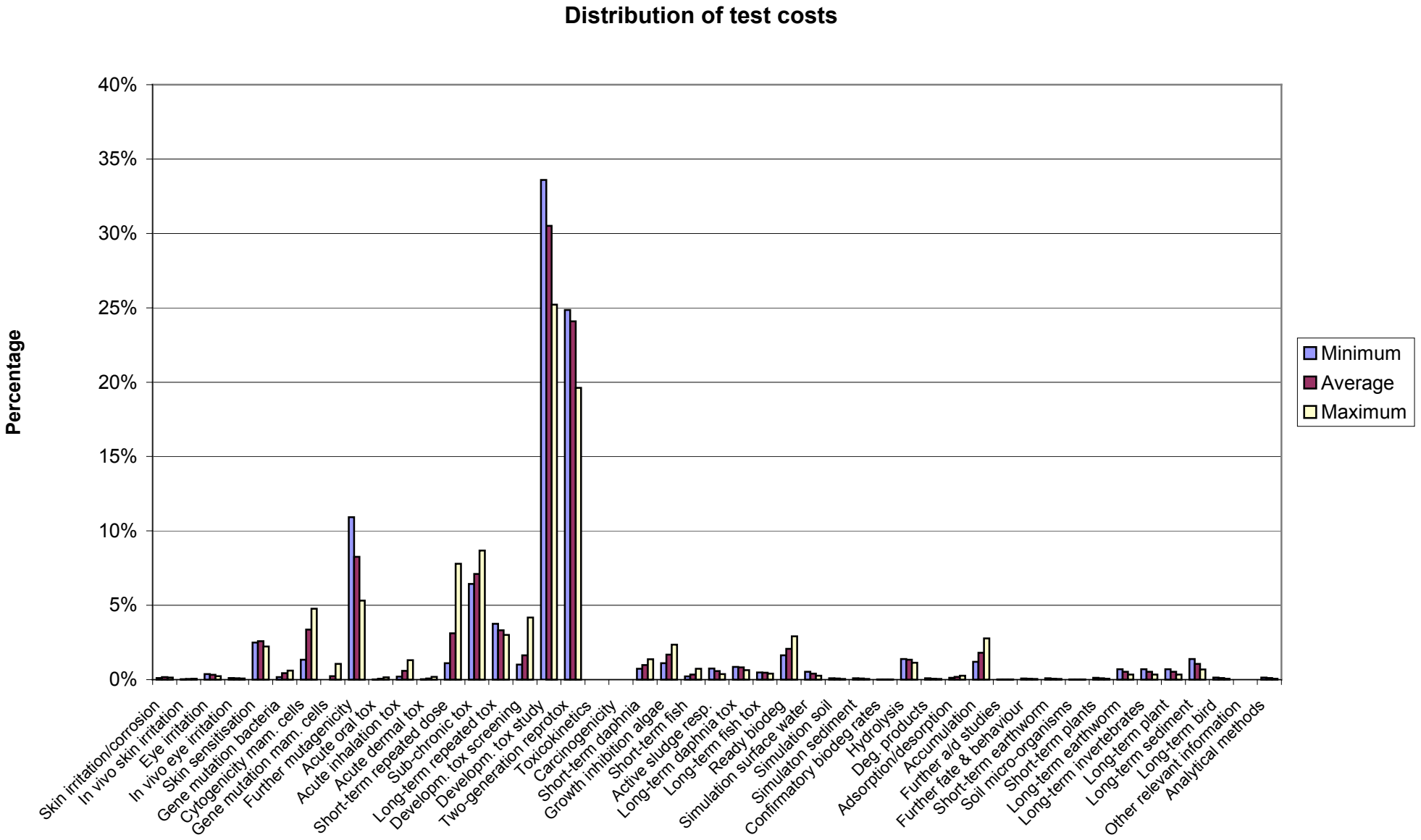
Long-term fish tox
Ready biodeg
Simulation surface water
Simulation soil
Simulaton sediment
Confirmatory biodeg rates
Hydrolysis
Deg. products
Adsorption/desorption
Accumulation
Further a/d studies
Further fate & behaviour
Short-term earthworm
Soil micro-organisms
Short-term plants
Long-term earthworm
Long-term invertebrates
Long-term plant
Long-term sediment
Long-term bird
Other relevant information
Analytical methods


Distribution of test costs
Percentage
40%
35%
30%
25%
20%
15%
10%
5%
0%
Minimum
Average
Maximum
Skin irritation/corrosion
In vivo skin irritation
Eye irritation
In vivo eye irritation
Skin sensitisation
Gene mutation bacteria
Cytogenicity mam. cells
Gene mutation mam. cells
Further mutagenicity
Acute oral tox
Acute inhalation tox
Acute dermal tox
Short-term repeated dose
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Long-term bird
Other relevant information
Analytical methods