



## READY FOR REACH?

### A Guide to Industry

#### I. SUMMARY

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) scheme will fundamentally change the manner in which chemicals are regulated and used throughout Europe. The regulation will require chemicals, both new and existing, placed on the market in Europe at above 1 tonne per annum to be registered. Those chemicals considered to represent the greatest hazard will be subject to evaluation and the most dangerous will be subject to authorisation, with possible restrictions on use.

It is very wide in its scope, covering all substances manufactured, supplied, used as intermediates or placed on the market, either on their own, in a preparation, or in an article, unless they are radioactive, subject to customs supervision, or are non-isolated intermediates. Waste is specifically exempted, as is food. Member States can exempt substances used in the interests of defence. Some other substances may also be exempt from parts of REACH and any substance regulated by other European Union (EU) legislation, such as biocidal and plant protection active ingredients.

Any new substance, *i.e.*, never before marketed in Europe, must undergo registration and supply can proceed three weeks after the registration date, unless the European Chemicals Agency (ECHA) advises that the registration is incomplete.

The regulation will have a phase-in period of some 11 years, with priority placed on high volume and chemicals that present a hazard to human health and/or the environment. There will be a six-month pre-registration period from the date that the ECHA is established, or one year after REACH enters into force on 1 June 2007, from which ECHA will establish a list of suppliers for each chemical pre-registered, with a view of industry forming consortia to share data and costs. Any supplier or user can voluntarily enter a chemical in the pre-registration phase with no commitment to proceed into full registration.

EU companies have the opportunity to retain anonymity by appointing a third party representative. Equally, non-EU companies can appoint an only representative. The regulation will apply in some form at each stage of the supply chain, including end users, formulators, and/or distributors, to categorise the risk and potential during lifecycle of a chemical.

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## II. BACKGROUND

The European Commission issued a much-discussed White Paper entitled “Strategy for a Future Chemicals Policy” on 13 February 2001 [1] intended to overhaul completely the EU chemicals legislation, and subsequently published the first draft of the proposed legislation on 7 May 2003: this is REACH.

During an 8-week Internet consultation, about 6,400 contributions were received from industry and regulators throughout the world. The final proposed Regulation was presented on 29 October 2003. These formal legislative proposals have been discussed by the Council of Ministers and the European Parliament, under the Co-decision Procedure. The European Parliament approved a compromise text developed by the UK Presidency on 17 November 2005, the Competitiveness Council reached political agreement on 13 December 2005, and the Common Position text was issued on 27 June 2006 [2].

A second reading of the legislation in the European Parliament was agreed on 18 December 2006, paving the way for REACH to enter into force on 1 June 2007, with ECHA being fully operational a year later. Meanwhile, work on the REACH Implementation Projects (RIP) continues, with specific development of the International Uniform Chemical Information Database (IUCLID) 5 software and guidance for industry. The new and existing substances regimes will continue until the REACH regime starts to become operational in 2008.

REACH will place a duty on companies that produce, import, and use chemicals in the EU to assess the risks arising from their use, and to take the necessary measures to manage any risks. Registration is needed to detail the properties, uses, and safe use of chemical substances. These registration requirements will vary depending on the volume in which a substance is produced, and on the likelihood of exposure to humans or the environment. There will be a phase-in period of 11 years to deal with existing substances.

Higher tonnage substances will require the most data, and will have to be registered first; lower tonnage substances would require less data and be registered later. All existing animal data must be shared to avoid repetition, and data older than 15 years will be freely available and the cost of “new” data shared.

The REACH system will be administered by the new ECHA in Helsinki.

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### III. REGISTRATION

All substances manufactured or imported in the EU at  $\geq 1$  tonne per annum will be registered with ECHA, who will assign a registration number and perform a completeness check using an automated process. The registrations are forwarded to Member State competent authorities and entered onto a database of registered substances.

Registration will be needed before new substances, *i.e.*, ones never before marketed in Europe, are manufactured or imported. Manufacture or import of new substances can begin three weeks after the registration date, unless ECHA informs the registrant that the registration is incomplete.

All substances on the European Inventory of Existing Chemical Substances (EINECS) must be registered in a phased review. Priority will be placed on substances of high total volume ( $> 1,000$  tonnes per annum throughout the EU as a whole) and those substances which are classified as Category 1 or 2 carcinogens, mutagens, or toxins for reproduction (CMR) or are hazardous for the environment, *i.e.*, persistent, bioaccumulative, and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances (*see* Table 1). Endocrine disruptors not covered by these criteria will be added to the list of very high concern substances on an *ad hoc* basis.

**Table 1 Criteria for Identification of PBT and vPvB**

Criterion	PBT criteria	vPvB criteria
P	Half-life $> 60$ d in marine water or $> 40$ d in fresh or estuarine water or half-life $> 180$ d in marine sediment or $> 120$ d in fresh or estuarine water sediment or half-life in soil $> 120$ d	Half-life $> 60$ d in marine, fresh, or estuarine water or $> 180$ d in marine, fresh, or estuarine water sediment or half-life in soil $> 180$ d
B	BCF $> 2,000$ in fresh or marine aquatic species	BCF $> 5,000$
T	Chronic NOEC $< 0.01$ mg/l for fresh or marine water organisms, Category 1 or 2 carcinogen or mutagen or Category 1, 2, or 3 toxic for reproduction or chronically toxic ( <i>i.e.</i> , classified as T or Xn with R48)	Not applicable
Note:	(a) BCF is bioconcentration factor, NOEC is no-observed effect concentration and CMR is a substance classified as carcinogenic, mutagenic, or toxic for reproduction.	

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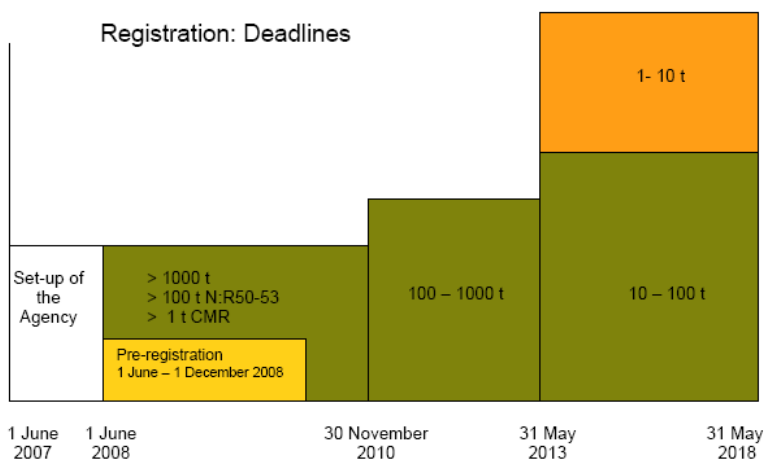
Criterion	PBT criteria	vPvB criteria
	(b) For marine environmental risk assessment, half-life data in freshwater sediment can be overruled by data obtained under marine conditions.	
	(c) Substances are classified when they fulfil the criteria for all three inherent properties for P, B, and T. There is certain flexibility, for instance in cases where one criterion is marginally not fulfilled but the others are exceeded considerably, however.	

The deadlines for registration of “phase-in” substances are based on the date the new Regulation comes into force (Table 2). A new manufacturer or importer of a phase-in substance can participate in the review and enter the EU market under the compromise text. It is important to note that new substances already notified under the current Dangerous Substances Directive (DSD) scheme are considered as registered under the new REACH system, but further information is required under REACH if the manufacture or import quantities are triggered. It is anticipated that *ca* 30,000 substances will be registered, with at least 10,000 requiring new testing.

Any supplier or user can be involved in the registration process.

EU manufacturers and importers can appoint a “third party” representative to retain anonymity of their details and non-EU manufacturers can appoint an “only representative” in the EU, who will represent the non-EU entity in Europe as well as the importers of the non-EU manufactured chemical.

**Table 2 Timings for Registration [3]**



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## **A. Registration Obligations**

Substances manufactured or imported, either neat or in a preparation, at > 1 tonne per annum, have to be registered, unless exempted. Some substances in articles are subject to registration, and the provisions have been clarified under the compromise text. Substances in articles, have to be registered only if they are classified as dangerous, are intended to be released from the article and are supplied at > 1 tonne per annum. Other substances in articles are not regulated. Under the compromise text, articles manufactured in the EU are treated the same as imports. ECHA can require a substance in an article to be registered if it poses a risk to human health or the environment.

Substances notified under the DSD [4] are considered as having been registered, as are active substances used only for products covered by the Plant Protection Products Directive [5] or the Biocidal Products Directive [6].

The REACH Regulation as a whole does not apply to radioactive substances, genetically modified organisms, substances in transit, or substances regulated by equivalent EU legislation (human and veterinary pharmaceuticals, food additives and flavourings, animal feed and substances used in animal nutrition). Furthermore, certain categories of substances are exempt from registration (Table 3).

**Table 3 Categories of Substances Exempt from Registration**

- |  |
|--|
| <ul style="list-style-type: none"><li>▪ The specific substances listed in Annex IV of the Regulation</li><li>▪ Substances covered by Annex V:<ul style="list-style-type: none"><li>– Radioactive substances</li><li>– Degradants from environmental factors</li><li>– Chemical degradants</li><li>– Products from use</li><li>– Products from reaction with additives</li><li>– By-products</li><li>– Hydrates, providing the anhydrous form is registered</li><li>– Non-dangerous natural substances</li><li>– Natural gas, crude oil, and coal</li></ul></li><li>▪ Monomers bound into polymers which are present at &lt; 2% (w/w) in the polymer or is supplied at &lt; 1 tonne per annum*</li><li>▪ Polymers</li><li>▪ Food and food ingredients</li></ul> |
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- Waste and certain recycled materials
- Minerals, ores, and ore concentrates
- Substances needed in the interests of defence

\* Registration is required for monomers present at  $\geq 2\%$  (w/w) in the polymer and supplied at  $\geq 1$  tonne per annum.

Intermediates are treated as a special category of chemicals. Non-isolated chemical intermediates, that are produced during synthesis and not intentionally removed from the synthesis equipment, do not have to be registered. Site isolated intermediates at  $\geq 1$  tonne per annum are registered with information on the identity of the manufacturer and substance, classification, and available test data.

Registration also applies for transported isolated intermediates, which are transported between or supplied to other sites under contractual control (including toll or contract manufacture) and for which there are strict conditions for manufacture and use to ensure only limited exposure. When transported at  $\geq 1$  tonne per annum, these are registered with the same information as site-isolated intermediates, but at  $> 1,000$  tonnes per annum, the basic Annex V test data are needed.

Although polymers do not have to be registered, if a polymer contains a non-registered monomer or other starting substance at  $\geq 2\%$  (w/w) in chemically bound form at  $\geq 1$  tonne per annum, this monomer or starting substance is regulated under REACH.

Substances used only for product and process-orientated research and development (PPORD) are exempt from registration for five years (extendable for a further five years on application in exceptional circumstances or ten years for substances used exclusively to develop human or veterinary medicines). The manufacturer or importer has to inform ECHA of the substance identity, labelling, and quantity and list the customers. The PPORD substance can only be used by those customers and it cannot be supplied to the public.

## **B. The Registration Dossier and Chemical Safety Report**

Annexes IV to VIII of the Regulation specify the information needed for registration. The general technical, commercial, and administrative information needed for all registrations for the technical dossier is specified in Annex IV (Table 4).

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**Table 4      General Annex IV Information Needed for Registration**

- |  |
|--|
| <ul style="list-style-type: none"><li>▪ Technical dossier (in a specified electronic format):<ul style="list-style-type: none"><li>– Annex IV technical data on the registrant, identification of the substance, manufacture, use, and guidance on safe use</li><li>– Robust summaries of safety data</li><li>– Proposed classification and labelling</li><li>– Statement whether animal testing was conducted</li><li>– Proposal for any further testing</li></ul></li><li>▪ Chemical Safety Report (CSR), for substances at &gt; 10 tonnes per annum. This is a risk assessment including PBT and vPvB assessment.</li></ul> |
|--|

The technical dossier, including robust summaries of the study reports, for registration of chemicals under REACH is to be submitted to ECHA electronically using the IUCLID format [7], which is a well-established database format for communicating and storing information on chemicals. The substance-related data are structured according to ten chapters, each of which has several subchapters.

A CSR is required for substances registered at 10 tonnes per annum and for PBT, vPvB, and CMR substances registered at 1 tonne per annum. This is a risk assessment, following the general provisions of Annex I of the proposed REACH Regulation. Substances that are used only to formulate cosmetics or to manufacture food-packaging materials are dual regulated -- they still have to be registered under REACH, although they are subject to separate EU measures that involve an evaluation of their safety to humans. Hence, in order to avoid duplication of work, the CSR for such substances only has to include an environmental risk assessment. There is additional guidance in Annex IB for substances that are components of preparations. The compromise text gives clarification on the CSR for special preparations, such as alloys. These general risk assessment principles correspond with the current EU practice for notified new substances and priority existing substances [8]. ECHA will develop software to help registrants prepare the CSR. It is essential to have input from downstream users to prepare the risk assessment for the CSR, which in practice may prove problematic. The CSR is a key element in communicating important safety information to users, and a summary of the CSR is to be included with the safety data sheet (SDS). The CSR also includes an assessment of whether the substance is classed as PBT or vPvB according to the Annex XII criteria (Table 1).



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### **C. Registration Safety Data**

The information on hazardous properties, as specified in Annexes VII to X, is linked to the manufacture/import level, on the grounds that there is a potential for more exposure as more substance is in the EU (Appendices 1-4). The Annexes specify the standard data requirements and give rules on the circumstances in which data may be omitted and when extra data are triggered. The compromise text agreed a targeted approach for registration of phase-in substances at 1 to 10 tonnes per annum. Full Annex VII test data are only needed if the phase-in substance meets the PBT or vPvB criteria, is classified as a CMR, or is classified as dangerous to human health or the environment and is for non-industrial use or intended to be released from consumer articles. Otherwise, only available safety data have to be included in the registration. New substances at 1 to 10 tonnes per annum require full Annex V data.

New animal studies are required only if surrogate data or *in vitro* alternative tests cannot provide the necessary information. All new studies are to be Good Laboratory Practice (GLP) compliant and conducted to the standard methods published in Annex X of the Regulation. Registrants have to update ECHA with any change in their status, or composition of the substance, significant changes in tonnage, new uses, significant new knowledge on risks, any change in classification and labelling, and any update to the CSR.

### **D. Non-Standard Data**

Any studies that are technically impossible can be omitted. Furthermore, the registrant can adapt the required standard information and provide the data using other information, such as non-standard or non-GLP tests, historical human data, a weight of evidence, structure activity relationships (SAR), or “read across” to tested analogues. Guidance on using such surrogate data is given in Annex XI of the Directive (Table 5). This includes a provision for “substance-tailored exposure-driven testing” to allow for reduced Annex VII and VIII animal testing for low exposure evaluated substances. The registrant is advised to gather and share existing information, consider the information needs, identify information gaps, and only then generate the missing data for registration at 1 or 10 tonnes per annum or propose further testing at 100 or 1,000 tonnes per annum.

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## **Table 5      Registration Safety Data**

- Annexes VII to X give standard data requirements (in column 1) and rules for omitting tests or additional studies (in column 2)
- Annex XI covers adapting the standard data requirements:
  - existing non-standard and/or non-GLP data
  - historical human data
  - weight of evidence
  - SAR
  - grouping and “read across”
  - data waivers, *i.e.*, study technically impossible
  - substance-tailored exposure driven testing

### **E.      Existing Studies and Literature Data**

In practice for many phase-in substances, there will be old studies or published papers that may be acceptable for the registration to assess the properties of the substance. Guidance on evaluating data for use under the EU chemical schemes is given in the Risk Assessment Technical Guidance Document [8]. It is important to evaluate existing studies with regard to their adequacy and completeness, especially where test standards vary. The adequacy of each test can be defined by two basic elements:

- **Reliability:** The inherent quality of a study relating to the test method, performance of the study, and the reporting (Table 6).
- **Relevance:** The extent to which a test is appropriate for a particular hazard or risk assessment.

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**Table 6 Factors to Consider When Evaluating the Reliability of an Existing Study**

- Purity/impurity and origin of the test substance.
- Complete test report is available or published in sufficient detail.
- Even if the reliability cannot be established or the study does not meet current standards, the data might still be used, taking into account:
  - Other studies or estimated results are consistent with the study results.
  - Other studies on close chemical analogues give similar results.
  - An approximate value is sufficient for use in the risk assessment
  - In the cases where differing results from similar studies were obtained or an extensive data set is available for an individual species or a taxonomic group, it may be possible to use the distribution of these data to draw general conclusions on the toxicity.

The reliability of the data is a key initial consideration and can be checked quickly to filter out unreliable studies, thus focusing on studies considered most reliable. Klimisch *et al* [9] have developed a scoring system for checking reliability (Table 7).

**Table 7 Klimisch Scoring Scheme for Reliability Studies**

**1 = reliable without restrictions:** “studies or data . . . generated according to generally valid and /or internationally accepted testing guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline . . . or in which all parameters described are closely related/comparable to a guideline method.”

**2 = reliable with restrictions:** “studies or data . . . (mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable.”

**3 = not reliable:** “studies or data . . . in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (*e.g.*, unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment.”

**4 = not assignable:** “studies or data . . . which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc).”

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## **F. Surrogate Data: Calculation, Read Across, and SAR/QSAR**

There are many methods to estimate physico-chemical properties and calculate those using thermodynamic and empirical relationships. Such predictions and calculations may be used in deciding which of the experimental methods or for providing an estimate or limit value where the experimental method cannot be applied for technical reasons. It is particularly important where estimation methods have been used, to ensure that the results derived are consistent with one another and are reasonable based on chemical structure. This is true for endpoints measured directly, as an unexpected result for the particular structure can lead to inconsistency and deficient data.

If there are no, or only limited, data available, Structure-Activity Relationships (SAR) may be considered, including quantitative SARs (QSAR). These can indicate a potential hazard, toxicokinetic properties, or the need for further testing. There are validated QSARs for some physico-chemical properties and for the ecotoxicity of certain chemical classes. SARs are not well developed in relation to mammalian toxicity, and “expert judgment” (perhaps based on “structural alerts”) is usually required.

The properties of substances can sometimes be assessed on a case-by-case basis using the “read across” approach. The properties of a substance are predicted from data on close analogues with similar physico-chemical properties and impurity profiles. Similar biological properties are anticipated, since toxicokinetics (especially absorption and metabolism) would be comparable. As many matching toxicological properties as possible are required to provide evidence in support of read across for missing endpoints.

The use of SAR and “read across” to form “categories” of chemicals for evaluation as a group is permitted in the International Council of Chemical Associations (ICCA) Organisation for Economic Co-operation and Development (OECD) high production volume (HPV) schemes and encouraged for U.S. HPV chemicals. There is guidance on SAR and categories in the OECD manual [10] and by the U.S. Environmental Protection Agency (EPA) [11], [12]. These established principles will be useful for registration of new and phase-in substances.

## **G. Data Protection, Data Sharing, and the One Substance One Registration Approach**

ECHA will establish and maintain a publicly accessible database of registered substances, with a short profile of hazardous properties, labelling, and other EU legislation that applies.

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The registrant can claim most information confidential (Table 8), and ECHA or Competent Authority who receives the information evaluates the confidentiality claim. Non-confidential information is made available to the public over the Internet. The compromise text gives improved measures for protecting information published on ECHA's website: the registrant can request that the robust summaries, study summaries, and supply tonnage band are not included in the public database, but this information would be available to the public on request.

### **Table 8      Confidentiality Provisions**

The registrant cannot claim confidentiality for:

- trade name and chemical name
- physico-chemical properties and the result of toxicology and ecotoxicology studies (and the determined Predicted No Effect Level/Predicted No Effect Concentration)
- purity and impurity (if relevant to classification)
- guidance on safe use
- non-confidential SDS information
- analytical methods for detection in humans or the environment
- fact that animal testing was conducted

Registrants can check the ECHA database before conducting animal studies, and also make a data-sharing enquiry to find out if a new substance has already been registered. If the substance has already been registered, studies submitted  $\geq 15$  years before can be used as of right for the new registration. Studies submitted less than 15 years before are still protected, but the two parties are put into contact with a view to reaching an agreement to share data. Animal studies cannot be repeated, and the idea of the scheme is for the second registrant to pay a proportion of the costs of the animal studies to their owner.

In order to allow the data-sharing scheme to operate for existing phase-in substances, there is a duty to pre-register such substances with ECHA within six months (or 12 months for small- and medium-sized enterprises (SME) and downstream users), beginning 12 months after the Regulation comes into force. The information in the pre-registration is the identity of the substance and registrant and a listing of the existing physico-chemical and safety data, including a short description of animal studies. There is also the option voluntarily to pre-register substances at  $< 1$  tonne per annum. All pre-registrants for a particular phase-in substance are participants in a substance information exchange forum (SIEF), and therefore the mandatory data-sharing/data-compensation scheme can operate for animal studies. If a particular study is not available within the SIEF, participants must

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reach an agreement to conduct a single study and avoid duplicate animal testing. A new supplier of a phase-in substance can begin supply and join the review programme.

The compromise text adopted the one substance one registration (OSOR) proposal: the aim is to have one lead registration dossier for a particular substance, with all other registrants referring to the lead submission to avoid repetition of labour at ECHA. There is the possibility of opting out of submitting a joint registration dossier if the cost would be disproportionate or where there would be a breach of confidentiality, however. Nevertheless, sharing of animal testing would still be mandatory, as would sharing of non-animal testing if requested by one potential registrant.

#### **IV. EVALUATION**

It is estimated that around 80% of the registered substances will not proceed to the next stage of evaluation. The registration information for the *ca* 6,000 substances exceeding a production or import volume of 100 tonnes per annum will have to be evaluated, however. National Competent Authorities will be allocated substances to evaluate on behalf of the EU, with input from ECHA. When the volume reaches 100 tonnes per annum, the manufacturer or importer has to submit the available information and a proposal for a testing programme (according to Annex IX of the Regulation). The rapporteur Competent Authority, in consultation with other Competent Authorities and ECHA, approves the final testing programme, and evaluates the studies when they are submitted.

At 1,000 tonnes per annum, an equivalent procedure is followed for Annex X testing.

For phase-in substances already exceeding the evaluation trigger values, a tiered approach is proposed following initial registration (Table 1).

#### **V. AUTHORISATION**

Substances of very high concern will have to be authorised before being used for specific purposes, which have been demonstrated to present a negligible risk. It is estimated that *ca* 1,500 substances will be subject to authorisation. There will be a published list of these very high concern substances, which are candidates for authorisation.

The first step is to identify existing substances, or particular uses of substances, requiring authorisation, and to decide on a deadline for authorisation and any uses exempted from

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authorisation. As additional very high concern substances are identified, largely from testing for registration and evaluation, they will be fed into the authorisation system.

Particular uses of very high concern substances will be authorised in the second step on the basis of a risk assessment covering all stages of the life-cycle for that particular use submitted by industry, including its ultimate disposal. The risk assessment will focus on exposure assessment for the use, and generally no new studies would be required. There is the possibility of authorisation based on adequate control of exposure, but not for PBTs, vPvBs, and “non-threshold” CMRs. ECHA, however, can take into account socio-economic factors in deciding if the use of the substance can nevertheless be authorised in the EU. The compromise text requires authorisations to be subject to time-limited review. It also gives greater emphasis to the substitution principle, and applications for authorisation have to be accompanied by an analysis of possible alternatives with their risks and the technical and economic feasibility of substitution.

## **VI. PREPARING FOR REACH**

The chemical industry operating in the EU will be greatly affected by REACH, and there will be ramifications worldwide. The uncertainty in key final aspects of REACH and how the scheme will be implemented make it challenging for industry to plan how to prepare for REACH and develop budgets for the costs of new studies and registration work. It is certain, however, that considerable resources will be needed. In practice, chemical companies should begin preparing for REACH as soon as possible to avoid being caught out by unanticipated costs, regulatory hurdles, and loss of business for important chemicals.

The overall initial cost of testing substances for registration under REACH depends on the tonnage, with data to be provided in advance of supply at  $\geq 1$  and  $\geq 10$  tonnes per annum. For supply at  $\geq 100$  and  $\geq 1,000$  tonnes per annum, the testing programme is negotiated with the Competent Authority, and hence the costs will be highly variable. In practice, there is likely to be ample opportunity to reduce testing costs by sharing data and making use of surrogate data and data waivers for many chemicals. There will be some cases where extra testing is triggered from the results of the standard tests or as an outcome of risk assessment, however.

Intelligent safety evaluation will be especially important for the new EU REACH scheme. Decisions have to be made on whether to use literature data and/or “surrogate data” and if “data waivers” are appropriate. With other registration schemes, there is the opportunity to consult the particular Competent Authority evaluating the substance before the registration dossier is submitted.

In accordance with REACH registrations, the dossier is submitted to ECHA, and initially there is only to be an administrative check. Therefore, it will probably be left to the registrant to decide on



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the final testing programme for new studies under REACH. Nevertheless, certain substances will be evaluated under the REACH scheme in detail by a rapporteur Competent Authority on behalf of the EU with a view to further testing. In these circumstances, it will be useful to base these discussions on the risk assessment included in the original registration in the CSR, supported by appropriate expert reports if necessary to improve the scientific arguments of the case.

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## **VII. REFERENCES**

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## **Appendix 1 Annex VII Data for Substances at $\geq 1$ Tonne Per Annum**

Melting/freezing point  
Boiling point  
Relative density  
Vapour pressure  
Surface tension  
Water solubility  
n-Octanol-water partition coefficient  
Flash point or flammability  
Explosivity  
Auto-flammability  
Oxidising properties  
Granulometry  
Acute oral toxicity  
Skin irritation or corrosivity evaluation or *in vitro* tests  
Eye irritation evaluation or *in vitro* test  
Skin sensitisation evaluation or local lymph node assay  
Ames test  
Acute *Daphnia* toxicity  
Algal growth test  
Ready biodegradation  
Possible additional studies:  
Further mutagenicity tests  
21-day *Daphnia* reproduction study



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## **Appendix 2 Annex VIII Data for Substances at $\geq 10$ Tonnes Per Annum**

In addition to the Annex VII data:

*In vivo* skin irritation (unless classified from Annex V data)

*In vivo* eye irritation (unless classified from Annex V data)

*In vitro* chromosome aberration test

*In vitro* gene mutation assay

Acute inhalation or dermal toxicity

28-day (or 90-day) repeat-dose study in the rat (normally oral exposure)

Developmental/reproductive toxicity screening study

Toxicokinetics assessment (a prediction based on the available data)

Acute fish toxicity

Activated sludge respiration inhibition test

Hydrolysis test

Adsorption/desorption screening test

Possible additional studies:

*In vivo* mutagenicity studies

Further repeat-dose study in the rat

Two-generation fertility study in the rat

Chronic fish toxicity study

Biodegradation simulation studies

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### **Appendix 3 Annex IX Data for Substances at $\geq 100$ Tonnes Per Annum**

The registrant makes a testing programme proposal covering:

- Stability in organic solvents and identification of degradants
- Dissociation constant
- Viscosity
- Reactivity to container material
- In vivo* mutagenicity studies
- 90-day repeat-dose study in the rat (if not part of the Annex VI data)
- Developmental toxicity studies in second species
- Two-generation fertility study in the rat
- 21-day *Daphnia* reproduction study
- Chronic fish toxicity study
- Simulation test on the ultimate degradation in surface water
- Soil simulation test
- Sediment simulation test
- Fish bioaccumulation study (unless there is a low predicted bioaccumulation potential, *e.g.*, from  $\text{Log } P_{ow} < 3$ )
- Further adsorption/desorption study
- 14-day earthworm toxicity
- Study of the effects on soil micro-organisms
- Short-term toxicity to plants



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#### **Appendix 4 Annex X Data for Substances at $\geq 1,000$ Tonnes Per Annum**

The registrant makes a testing programme covering, if appropriate:

Further mutagenicity studies

Long-term repeat-dose ( $\geq 12$  months) study in the rat

Further toxicity study to investigate specific concerns

Two-generation fertility study in the rat (if not part of the Annex VII data)

Carcinogenicity study (often combined with a 2-year chronic toxicity study, usually in the rat)

Further biodegradation in water, sediment, and soil -- covering degradation rate and identification of relevant degradants

Further environmental fate and behaviour studies

Long-term earthworm toxicity

Long-term toxicity to other soil invertebrates

Long-term plant toxicity

Long-term toxicity to sediment organisms

Long-term or reproductive bird toxicity