

REACH - Minimisation of Animal Testing

This leaflet provides a brief summary of the opportunities that are available to registrants to minimise animal testing.

What is REACH?

REACH (Registration, Evaluation, Authorisation and restriction of CHemicals) is the new system for controlling chemicals in Europe. It became law in the UK on 1 June 2007.

Minimisation of animal testing

When considering how to fulfil the REACH information requirements, opportunities are available to registrants to minimise animal testing and reduce costs.

Current estimates suggest that around 5-10,000, substances will be registered by the 1st of December 2010 deadline. For a single substance, with no pre-existing data, and no attempt to minimise animal testing, registration and subsequent fulfilment of the information gaps could require over 5000 animals, assuming little or no avian testing. The REACH regulation provides opportunities to reduce costs and register effectively using fewer animals than predicted.

Article 13(4) of REACH stipulates that toxicological and ecotoxicological tests shall be carried out in compliance with EU Directive 86/609/EEC on animal protection. This Directive provides basic requirements for the care and accommodation of laboratory animals, and stipulates that experiments shall be designed to avoid distress and unnecessary pain and suffering to the animal. Furthermore, experiments should not be performed if the results can be obtained by another scientifically satisfactory method. Directive 86/609/EEC is currently under revision. The Animals (Scientific Procedures) Act 1986 (as amended) transposes Directive 86/609/EEC into UK law, and provides the regulatory framework for controlling animal testing in the UK.

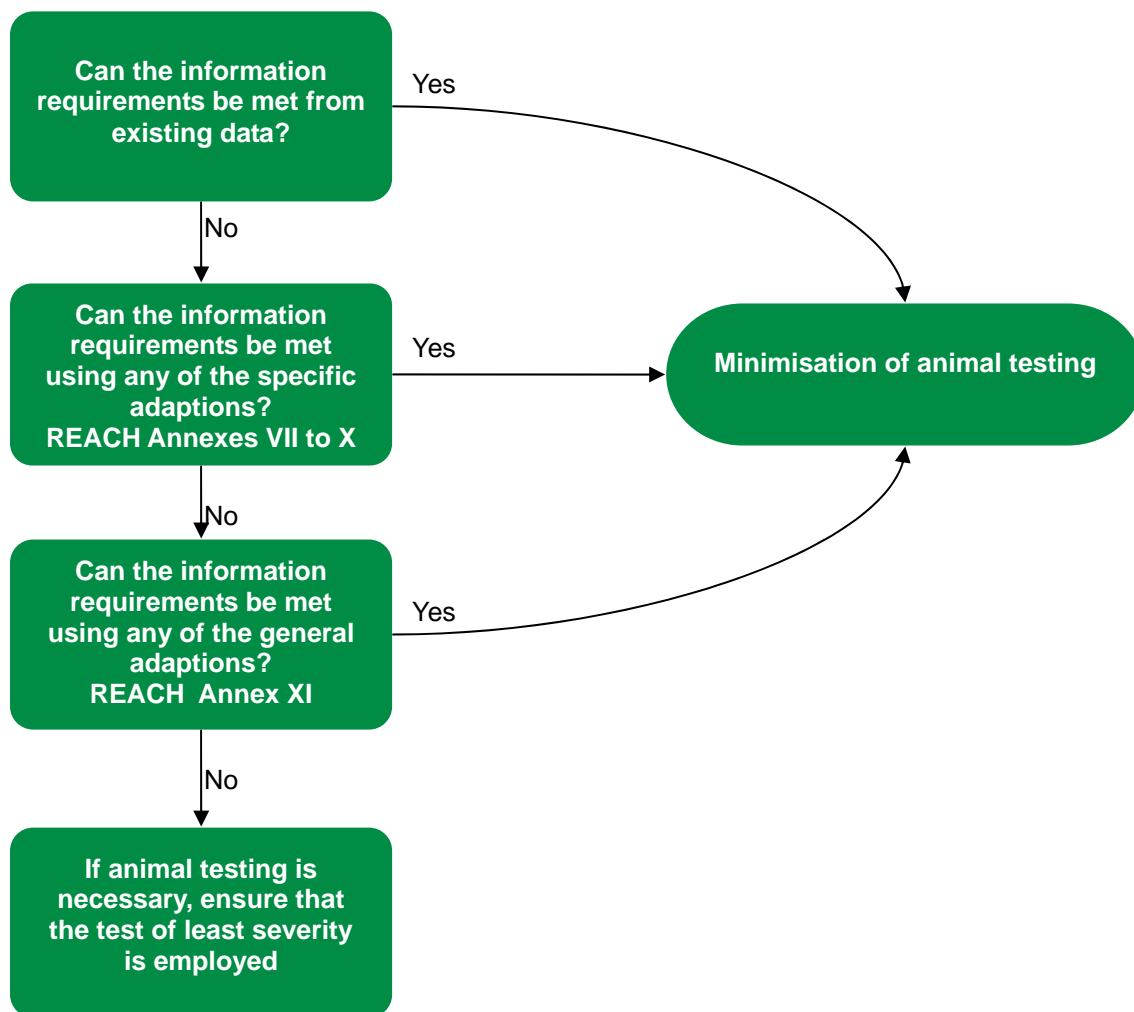
Where possible, scientifically sound approaches to the implementation of the 3Rs (reduction, refinement or replacement of animal use) which are already stipulated under the REACH Regulation, should be used. This is particularly important as the registration deadline for the highest tonnage substances is fast approaching, and it is very unlikely that complete replacements for remaining toxicity endpoints will be available in time. There are Annexes in the REACH legislation (Annexes VII to XI) that provide information and guidance on the adaption (waiving) of animal tests. ECHA has provided some further guidance to help; the most relevant is the REACH guidance on information requirements and Chemical Safety Assessment (CSA)¹.

Key messages for registrants

- 1 Before concluding that there is a toxicity information gap, the Substance Information Exchange Forum (SIEF) should consider all the available existing information.
- 2 Consider whether animal testing can be minimised by following one or more of the specific testing adaptations provided in the REACH regulation itself, see Part 1 (below).
- 3 If no specific adaptations are applicable, consider whether animal testing can be minimised in other more general ways *in-lieu* of testing - see Part 2 (below).
- 4 If adaptation is not possible, and a new animal test is required, ensure that the test of least severity and using the fewest animals is employed. The test should be that expected to cause the least pain, suffering, distress and lasting harm.

These are illustrated in the diagram overleaf:

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The UK Competent Authority recommends that the duty holders who are compiling registration dossiers consider whether these approaches to the minimisation of animal testing will be of relevance to them

Part 1: Opportunities for minimising new animal testing - REACH Annexes VII-X

The standard REACH information requirements can be found in column 1 of the tables in Annexes VII to X. In column 2 there are rules for adaptation (“waiving”) of the tests specified in column 1. These rules outline circumstances in which a particular information requirement involving a vertebrate animal test may be modified. There are many specific rules, and some of the key ones are detailed in Table 1, below. Most significantly, there are derogations for: the *in-vivo* tests for skin irritation, postponement of the two generation reproductive toxicity study, and circumstances for waiving of the short-term repeated dose and reproductive toxicity studies.

Positive findings from isolated eye tests for detecting severe eye irritants are acceptable. However, negative findings in such a test should be followed by an *in-vivo* eye irritation test because a negative finding cannot be used to distinguish between eye irritants and non irritants. For further information see REACH end point specific guidance², chapter R 7.2.3.1 There are two test guidelines describing isolated eye protocols (Organisation for Economic Cooperation and Development (OECD) Test Guidelines 437 and 438) but these are limited to specific chemical classes. The validation status of alternative tests is subject to regular changes, and those commissioning tests should take account of this by checking their current status.

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Table 1: Specific opportunities for minimising new animal testing (Annex VII to X)

Opportunities to adapt tests - Annex VII (1-10 tonnes/annum)	
Skin sensitisation	<p>The test need not be conducted if the substance is classified as corrosive, or a skin sensitiser, or flammable in air at room temperature.</p> <p>The study of choice is the Local Lymph Node Assay (LLNA – OECD TG 429), with justification needed for guinea pig tests. It is possible to use the reduced LLNA protocol, but this does not give information on potency. There is no internationally agreed reduced LLNA protocol available currently.</p>
Acute oral toxicity	<p>The test does not need to be conducted if the substance is corrosive, or if an acute inhalation toxicity study is available.</p>
Opportunities to adapt tests - Annex VIII (10-100 tonnes/annum)	
Skin irritation	<p>It is now possible to conduct skin irritation <i>in-vitro</i>, Method B46 in the Test Methods Regulation (440/2008/EEC). Both positive and negative findings are acceptable. Registrants are encouraged to conduct the <i>in-vitro</i> tests wherever possible.</p>
Eye irritation	<p>Testing does not need to be conducted if the substance is corrosive or flammable in air at room temperature. If testing is necessary, consider conducting an <i>ex-vivo</i> test for severe eye irritation².</p>
Repeat dose and reproductive toxicity	<p>If both repeated dose toxicity and reproductive toxicity studies need to be conducted:</p> <p>(a) For substances up to 100 tonnes/annum: conduct the “combined” study (OECD TG 422) to save animal numbers.</p> <p>(b) For substances at 100 tonnes/annum or more: propose standard reproductive and developmental toxicity studies, and long term repeated dose toxicity studies, and do not conduct any shorter-term studies for these end points. However, the CSR should indicate the interim risk-management measures downstream users should take before the findings from the proposed studies are included.</p>
Short-term toxicity to fish	<p>Testing does not need to be conducted if the substance has very low solubility in water or is unlikely to cross biological barriers. Or if a long-term fish toxicity study is available. The threshold approach for acute fish toxicity³ should be used where possible, if a test is needed.</p>
Opportunities to adapt tests - Annex IX (100-1000 tonnes/annum)	
Reproductive study	<p>The requirement for a two generation study (OECD TG 416) should be considered at 100 tonnes/annum (Annex IX) if adverse effects on the reproductive tissues are observed in the available repeated dose studies. Where no such adverse effects are observed, the 2-generation study would only need to be conducted if the tonnage reached 1000+ tonnes/annum.</p>

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Opportunities to adapt tests - Annexes IX and X (100-1000 and 1000+ tonnes/annum)	
Long term fish toxicity	Need not be proposed unless required to clarify risks.
Bioaccumulation in fish	Need not be proposed if the substance has a low potential for bioaccumulation (for instance a log Kow < 3) and/or a low potential to cross biological membranes; or – direct and indirect exposure of the aquatic compartment is unlikely
Long-term reproductive toxicity to birds	Need not be proposed if risks to predatory birds can be assessed using mammalian toxicity data.

Note: more detailed information is available in the REACH end point specific guidance²

Part 2: Opportunities for minimising new animal testing – REACH Annex XI

The UK REACH CA encourages duty holders to consider the extent to which Annex XI of REACH might apply to them. This Annex provides general rules that registrants may use to adapt (“waive”) the standard testing regime set out in Annexes VII to X and thereby minimise new animal testing. These rules can be applied individually or in a weight of evidence argument *in-lieu* of new animal testing.

For Annexes VII and VIII, the adapted information should be included directly in the registration dossier, and will not be compliance-checked routinely by the European Chemical Agency (ECHA). However, for Annexes IX and X it is a testing proposal that will be required, rather than the adapted information itself. These proposals will be subject to a formal evaluation by ECHA, who will judge whether an adaptation or a standard test should eventually be submitted.

Use of existing data

REACH requires that new studies should be conducted in a Good Laboratory Practice (GLP) accredited laboratory. However, the same standard does not apply to pre-existing studies, i.e., pre existing studies need not have been conducted in a GLP environment. The minimum requirement is that the study is of sufficient quality to enable a decision on classification and labelling to be made and/or a CSA to be conducted. A useful “rule of thumb” in judging quality is to look at the relevant international standard (OECD⁴ or EU⁵) and consider how closely the old study matches. It should be noted that if an old study does not reveal a hazard it should not automatically be disregarded.

It has been suggested that it may be possible to estimate a LD(C)50 value (a dose or concentration that kills half the test animals after a single exposure) from existing repeated dose studies (28/90-day studies) if the relevant acute toxicity study is missing. In principle this is possible, but only if mortalities are observed during the early part of the study, say after 2-3 exposures/doses. The later in the study mortalities are observed the more difficult it becomes to consider them to be acute lethality. The same approach could be taken with early clinical signs of toxicity, which could be used to estimate the level of evident toxicity, which is the stopping point for the fixed dose procedure (OECD TG 420). The critical factor is that the clinical signs should be observed very early in the study.

Weight of evidence assessment

This is a common scientific practice which can be applied when a conclusion on the presence/absence of a hazardous property cannot be made on information from a single source alone. For example, there could be information from a number of studies, none of which were conducted to recognised international standards. However, when taken together can be used to meet the REACH information requirements and be sufficient for a CSA.

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A weight of evidence approach is a very efficient way of maximising the potential of older studies, and avoiding new animal testing for a particular hazardous property

(Quantitative) structure activity relationships

(Q)SARs are computer-based models which are designed to predict the physico-chemical properties, potential human health and environmental effects of a substance from knowledge of its chemical structure. In principle, the results from validated (Q)SARs could be used to fulfil one or more of the REACH information requirements or help build chemical categories without the need to use animal tests. Further information on the application of (Q)SARs can be found in Chapter 6 of the REACH guidance on information requirements and chemical safety assessments⁶.

A prospective new tool for use by potential registrants is the OECD (Q)SAR application toolbox⁷ which is being jointly developed by the OECD and ECHA. The toolbox is regarded as an essential tool for helping pre-registrants obtain relevant information on the intrinsic hazards of their substances.

On a cautionary note, however, the substance in question should fall in the “applicability domain” of the model, the results will have to be adequate for the purpose of classification and labelling and/or risk assessment, and adequate and reliable documentation of the model will need to be provided. It is anticipated that (Q)SARs will play an increasing role for later registrations, in 2013 and 2018, as information from the 2010 registrations is used to refine the existing (Q)SARs.

Grouping and read across

Where substances share structural similarities or share common metabolic pathways they can be grouped together in a chemical category. Categories of chemicals are selected on the assumption that the properties of a series of chemicals with common structural features will show similar trends in their physico-chemical properties, and more importantly, in their toxicological (human health/ecotoxicity) effects or environmental fate properties. Common behaviour or consistent trends are generally associated with a common underlying mode of action.

Once a group has been established, it is possible to use information from the data rich members to fill data gaps by the process of read-across. This can be either qualitative, in which the presence (or absence) of a particular hazard is predicted, or quantitative in which the magnitude of a particular property is predicted; for example, a No Observed Adverse Effect Level (NOAEL– a dose or concentration at which no adverse changes are observed). It is important to ensure the category has a scientifically sound basis and that all hazards are read across, both positive and negative.

There is a lot of experience of developing and applying chemical categories in a regulatory context, for example in the OECD High Production Volume Chemical (HPV) programme. This experience has been adapted by the EU for REACH (Section 6.1 of the REACH guidance on information requirements and chemical safety assessments).

In vitro methods

In some instances, information from *in-vitro* tests may be used for hazard identification and as part of a CSA. For a positive outcome only, a test is considered acceptable if it meets the European Centre for the Validation of Alternative Methods (ECVAM) criteria for acceptance into the pre-validation process (ECVAM - <http://ecvam.jrc.it/>). For negative outcomes to be accepted; the test must have been scientifically validated, the results should be adequate for classification and labelling and/or use in a CSA, and adequate documentation is available.

Where *in-vitro* tests have been successfully validated and adopted into the REACH Test Methods Regulation (EC 440/2008), these should be used in preference to the equivalent *in-vivo* test.

Testing is not technically possible

It is possible to adapt some tests if it is not technically possible to conduct the test, or the substance is very hazardous, for example the generation of an explosive atmosphere. The REACH Test Methods Regulation should also be consulted, as some test methods, such as the acute dermal and acute inhalation tests identify specific circumstances where testing is inappropriate.

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Exposure-based waiving

Exposure-based waiving of certain tests may be permitted in cases where it can be shown that exposure is insignificant or absent for the substance concerned. This will depend on the conditions of use and is outside of the scope of this document.

Application of the 3Rs (reduction, refinement and replacement)

Directive 86/609/EEC indicates that “Experiments must not be done if another that replaces, reduces or refines the existing test is reasonably and practically available” This means that where there is a choice of tests for a particular end point, the test of least severity should be used. This applies to; testing for skin sensitisation where REACH specifies that the Local Lymph Node test (LLNA – OECD TG 429) is the preferred test and to acute oral toxicity where the Fixed Dose Procedure (OECD TG 420) appears to offer some animal welfare advantages over the other available test methods. The development of *in-vitro* testing for skin irritation and corrosivity has progressed to the point where both parts of the *in-vivo* test can now be completed *in-vitro*. Therefore the *in-vitro* test should now be the method of choice.

Further information

Detailed guidance is available on the ECHA's REACH website (http://echa.europa.eu/reach_en.asp) and further information from the UK Competent Authority can be found at (<http://www.hse.gov.uk/reach/>).

For general advice on the application of REACH obligations, you can contact the UK REACH Competent Authority's helpdesk: by email: UKREACHCA@hse.gsi.gov.uk.

Website links referred to in this leaflet

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- ¹ REACH http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r2_en.pdf
- ² REACH http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r7a_en.pdf
- ³ OECD <http://www.oecd.org/dataoecd/44/12/40985084.pdf>
- ⁴ OECD http://titania.sourceoecd.org/vl=1350577/cl=25/nw=1/rpsv/periodical/p15_about.htm?jnlissn=1607310x
- ⁵ European Union <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:142:0001:0739:EN:PDF>
- ⁶ REACH http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r6_en.pdf
- ⁷ OECD http://www.oecd.org/document/54/0,3343,en_2649_34379_42923638_1_1_1_1,00.html

