

Factsheet

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Role of animal testing in ensuring the safe use of chemical substances

It is the goal of the REACH Regulation to ensure a high level of protection of human health and the environment from hazardous effects of chemicals. The REACH Regulation represents the balance established in the legislative process between the need for generating new information on hazardous properties using animal tests and the aim of avoiding unnecessary animal testing. It therefore establishes the principle that testing on vertebrate animals shall be a last resort.

Companies producing or importing chemical substances have to ensure that they can be used safely. This is achieved by using – and where necessary generating – information on the intrinsic properties of substances to assess their hazards both for classification and risk assessment, and hence to develop appropriate risk management measures to protect human health and the environment.

A key motivation for developing REACH was to fill information gaps for the large number of substances already in use in the EU, as for many such substances there was inadequate information on their hazardous properties and the risks their use may pose.

Without a comprehensive set of information on the essential hazardous properties of higher volume chemical substances, registrants cannot undertake a chemical safety assessment that will recommend appropriate risk management measures to avoid or limit exposure. In particular, information on properties such as organ toxicity after long term exposure, the potential to induce cancer, toxicity to the developing foetus, toxicity to the reproductive functions, or long term aquatic toxicity are often not available for such substances.

STANDARD INFORMATION REQUIREMENTS

REACH registrants have to provide all relevant and available information on the intrinsic properties of the substance in their registration dossier.

The information which must be provided in a company's registration dossier depends on the tonnage level at which a substance is imported or produced. Higher tonnages of a substance are regarded as an indicator of a higher potential to cause damage to human health and the environment and need to be investigated more thoroughly than at lower tonnages.

Annexes VII, VIII, IX and X of the Regulation specify what information is required at levels of 1, 10, 100, or 1000 or more tonnes per year per registrant, respectively. These are called the 'standard

information requirements' and are highest for substances at or above 1000 tonnes per year.

Where data for a basic ("core") set of information which addresses a number of intrinsic properties of a substance (as specified in Annexes VII and VIII) is not available, registrants are responsible for generating this data and providing it in their registration dossier. Depending on the property concerned, the standard information requirements may specify information which can be obtained from standard tests. Depending on the test specified either bacteria, cultured cells or animals are normally used.

The core information is intended to show, for example, if a single exposure, or one lasting a few hours or days, has the potential to cause serious harm to human health or the environment. Information from other tests, in bacterial cells for example, may be able to give an indication as to the potential of a substance to cause cancer.

At higher tonnage levels, there are additional information requirements (as specified in Annexes IX and X). At these levels, more detailed and extensive information is required and can be obtained using what are called higher-tier studies. If data gaps have been identified and cannot be filled otherwise, registrants will have to conduct higher-tier studies to fulfil the requirements of Annexes IX and X. However, before such testing can start, they have to submit testing proposals and receive prior approval from ECHA.

Some of the studies to assess the properties of substances, specifically for high tonnage registrations, are conducted on experimental animals. For most of the hazardous properties studied in experimental animals, the species used are rat and mouse, but rabbit, guinea pig, fish, and in rare cases bird, may also be used (specifically bred strains).

REACH however requires that tests entailing the use of live animals shall be carried out in compliance with legislation enacted under Directive 2010/63/EU on the protection of animals used for scientific purposes. This Directive covers a number of requirements on the care for laboratory animals and requires that scientifically satisfactory methods or strategies using live animals should not be performed if the results can be obtained by another scientifically satisfactory method. The test method regulation (EC

No 440/2008) is the vehicle for the Commission to lay down test methods to be used under REACH.

There are a number of options to use information derived from other 'non-standard' methods or other non-testing approaches, which are described below in the following sections.

AVOIDING UNNECESSARY TESTING ON ANIMALS

There are several different mechanisms in REACH to avoid unnecessary animal tests, in particular, data sharing and the use of alternative test methods and other approaches to predict the properties of substances. However, the filling of data gaps means that some new animal testing will be necessary.

Registrants are obliged by REACH to limit new studies using vertebrate animals for REACH registration as they are to be conducted only as a last resort. Registrants must first collect and assess all existing data. They then have to identify data gaps and consider whether these can be filled by using either *in vitro/ex vivo* studies or other alternative approaches including prediction methods before any new animal tests are conducted.

This means that all available information is collected: information from *in vivo* (using live animals), *ex vivo* (for example, using tissues from animals) and *in vitro* studies (for example, using bacteria or cultured cells), information from human exposure, predictions on the basis of information available from structurally-related substances (i.e. by 'read-across' and 'chemical categories') and predictions from valid computational prediction methods, for example, (quantitative) structure activity relationships ((Q)SAR).

To justify the use of non-standard tests or other non-animal testing approaches, registrants may 'adapt' the standard information requirements by complying with a number of preconditions (as specified in Annexes VII to X, column 2 or Annex XI of the Regulation). Annex XI enables the use of any information, even that not generated by recognised test methods, which avoids or reduces the need for animal testing, it must also be suitable for the purposes of classification, risk assessment, and hazard communication.

In addition, there are data sharing obligations for registrants of the same substance to avoid duplicate testing using experimental animals.

Registrants remain responsible for assessing the intrinsic properties of their substances for hazard and/or risk assessment and classification; they are responsible for making the respective technical and scientific judgments. However, ECHA can require missing information to be provided, including animal tests, if the adaptation justification or non-standard data do not meet the information needed according to REACH, as an outcome of the dossier evaluation processes.

The objectives in defining ECHA's role in evaluation under REACH is to keep the responsibility for safety of chemicals on industry whilst avoiding unnecessary testing. ECHA performs compliance checks of registration dossiers to verify whether the information requirements of the REACH Annexes are met. ECHA's role in evaluating testing proposals is to ensure that if a test is performed the results will be acceptable for REACH purposes. In this process, ECHA is not expected to do any work that should normally be done by the registrant. In both cases, the result may be a draft decision requesting further information including results from tests on animals.

On its website, ECHA publishes all testing proposals involving vertebrate animals which are put forward by registrants with a view to fulfilling the standard information requirements specified in Annexes IX and X of REACH. These concern the higher-tier studies for complex endpoints which require most animals. Third parties, such as non-governmental organisations and companies, then have 45 days to submit scientifically-valid information or studies that address the relevant substance and hazard end-point specified in the Testing Proposal.

The companies that are addressed by ECHA's draft decisions, have the right to comment in the decision making process. The Member States Competent Authorities review all draft decisions and may propose amendments. If so, the case is referred to the Member State Committee, which has to reach a unanimous agreement on the draft decision. If this is not reached, ECHA refers the case to the Commission for decision. This procedure was established to ensure that the best possible use is made of existing information, and that animal testing is required only when the necessary information is unavailable.

The Classification, Labelling and Packaging (CLP) Regulation does not require new studies to be conducted, although some suppliers of substances

may choose to do this. Industry has to obtain all the available relevant information and evaluate it using the CLP classification criteria, in order to appropriately classify their chemical substances and mixtures for hazard communication by means of labelling, providing Safety Data Sheets (SDSs) and using suitable packaging. In practice, this means that many substances can be (re)classified on the basis of the REACH registration data.

CURRENT STATUS OF ALTERNATIVE APPROACHES

Over the past few years a number of *in vitro* test methods that are suitable for REACH purposes have been adopted and incorporated in the Test Methods Regulation. However, there are currently no *in vitro/ex vivo* tests or test batteries that can act as a like-for-like replacement of higher-tier toxicology studies, such as those investigating carcinogenicity, mutagenicity or reproductive toxicity (CMR), for REACH. However, they may be useful as part of a weight of evidence (WoE) approach or as a basis for classification under CLP and can thus, depending on the case, render testing on animals unnecessary.

Animal tests can be avoided if the hazardous properties of a substance can be predicted using computer models, sometimes referred to as *in silico* methods, i.e. using QSARs or the SAR approach. At present, such *in silico* predictions cannot be used alone to predict a number of the toxicological properties (long-term toxicity, carcinogenicity, mutagenicity, and reproductive toxicity) of substances for REACH, although they may be useful as part of a WoE approach or as a basis for classification under CLP.

Properties of substances can be predicted using information from tests on analogues by the 'read-across' approach, or for a group of substances using the 'category' approach. The registrant is responsible for making the scientific arguments that these predicted properties are adequate for REACH, in terms of providing comparable information to the animal studies on the registered substance. Read-across and categories are the most promising approaches to predict the long-term toxicological and CMR properties of substances for REACH (and CLP). However, it should be noted that sufficient information must be available to support these predictions.

Registrants should be careful in using tools developed in research and development projects and other

innovative techniques for predicting properties and data waiving as these are not necessarily suitable as regulatory tools for REACH and CLP. Registrants are advised to be mindful of the limitations from such predictions, which will depend on the particular model used and may be case-specific. Nevertheless, it may be that non-standard and innovative predictions can serve to build up a fuller picture of the substance property as part of a WoE approach or as part of an Integrated Testing Strategy (ITS), even if the property cannot be predicted adequately for REACH and CLP using the technique alone.

Furthermore, newly-developed alternative *in vitro* test methods undergo validation in order to assess their relevance and reliability. The European Centre for the Validation of Alternative Methods (ECVAM) validates alternative methods that replace, reduce and refine the use of animals in scientific procedures. Regulatory acceptance of validated alternative methods will be facilitated and streamlined by the new mechanism of “preliminary analysis of regulatory relevance” (PARERE). These consultation networks of the European Commission involve EU Member State contact points and relevant agencies and committees, such as ECHA.

PROMOTING ALTERNATIVE METHODS FOR ANIMAL TESTING

Besides its role in the compliance check and the testing proposal examination, ECHA has a role to play in helping registrants to implement REACH and by facilitating the duties of the various actors in meeting the legislative requirements, which balance the need to assess the risks of substances to human health and the environment and to avoid unnecessary animal testing. ECHA also promotes alternatives to testing on animals that meet the regulatory needs, by providing information on the opportunities and limitations of alternative test methods and other approaches.

This is part of the day-to-day activities of the Agency:

- ECHA facilitates and promotes the formation of Substance Information Exchange Fora (SIEFs) where companies share existing data, for example available data from animal tests.
- ECHA has developed a practical guide “How to avoid animal testing” and a series of guidance documents to support registrants in data sharing, chemical safety assessment and other REACH

related tasks that can help to avoid unnecessary animal tests.

- ECHA Annual Progress Reports on Evaluation provides recommendations for improving the quality of registrations. to help ensure chemical substances can be used safely and that unnecessary animal testing is avoided.
- A specific report on the “Use of Alternatives to Testing on Animals for the REACH Regulation” is published by ECHA every three years.
- The unique set of information collected through registration and published on the ECHA dissemination website can help future registrants to identify existing data, could encourage data sharing and may facilitate further developments of prediction methods.
- ECHA hosts the eChemPortal, which provides free public access to information on properties of chemicals and direct links to collections of information prepared for government chemical review programmes at national, regional, and international levels. ECHA uses this information to verify if information on animal tests are already available from other authorities.
- The OECD QSAR Toolbox is an important tool for supporting and enabling category building. ECHA contributes actively to the further development of the Toolbox.
- The ECHA Helpdesk deals with enquiries on information requirements, computer modelling (Q)SARs, read-across, adaptation rules and testing proposals.
- ECHA is listening to the concerns of animal welfare organisations and engaging stakeholders in its work. The Agency organises targeted awareness raising and stakeholder support activities, including workshops, Stakeholder Days, webinars and other web-based information and tools.
- The development of internationally-agreed alternative test methods is especially important for avoiding unnecessary animal testing, since they standardises the study protocols. ECHA contributes to such developments by participating in EU and OECD working groups, and maintaining links with other important actors, such as the Member States, the Joint Research Centre of the European Commission and other EU agencies involved in risk assessment of chemicals.

Animal testing under REACH:

<http://echa.europa.eu/web/guest/chemicals-in-our-life/animal-testing-under-reach>